THE VALUE OF ELECTROCARDIOGRAPHY WHEN CORONARY-ARTERY DISEASE IS SUSPECTED

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As the years go by, electrocardiography becomes both increasingly complex and increasingly popular. As it is a highly specialised procedure which the ordinary doctor must accept on trust, it could reasonably be expected that from time to time a critical analysis of its value would appear in the medical journals. But it seems that eminent cardiologists have thought it prudent to maintain a discreet silence on this matter. This lack of guidance from the cardiologists is my excuse for writing this paper. If the conclusions reached are at variance with their usual teachings, perhaps one of them will make a detailed reply to my errors.

The situations in which it may be hoped that help will be given by electrocardiography may be grouped under the following five heads:

1. When the patient gives a typical story of angina of effort.
2. When the patient has recurrent attacks of chest pain of an indeterminate nature.
3. When the patient may have emotional cardiovascular symptoms.
4. When the patient has had pain or other symptoms which may be due to cardiac infarction.
5. When routine electrocardiography is done to give information about the heart for employment, life assurance, and other purposes.

Patients

TYPICAL ANGINA OF EFFORT

Here, it is assumed that pain always develops somewhere in the upper part of the body with a certain amount of exertion, and rapidly disappears on rest. The pain is usually in the mid-chest; but it may spread to one or other arm, the back, or the lower jaw, or it sometimes starts in the arms. Exertion after a meal results in the earlier-than-usual development of pain. Emotion may also bring on the pain. Trinitrini taken before exertion postpones or prevents the pain.

This story is, by definition, "angina of effort" or "angina pectoris". The only way of determining whether a patient has this particular kind of pain is by talking to him; the E.C.G. or any other objective means of examination can neither confirm nor deny that this pain is felt. Can the E.C.G., therefore, yield information about the pathological process responsible for the pain, or about the prognosis?

The immediate basis of angina of effort is thought to be myocardial ischæmia. By far its commonest cause is, without doubt, coronary-artery disease. Other causes are anæmia, syphilitic aortitis, and aortic stenosis. The E.C.G. is of little or no value in identifying these rarer conditions.

When angina is due to coronary-artery disease, the E.C.G. is sometimes normal, and sometimes reveals various abnormalities, such as left axis-deviation or evidence of old infarction or of bundle branch block. The E.C.G. which is normal at rest may become abnormal after the patient has exercised. Many studies have shown that the prognosis is worse when the E.C.G. is abnormal than when it is normal. Block et al. (1952), for example, in observations on nearly 7000 cases, have clearly demonstrated that this is so, and that some E.C.G. abnormalities have a worse prognosis than others. But the prognosis also depends on other factors, such as the severity and rate of worsening of the pain, the size of the heart, the level of blood-pressure, and the association of congestive heart-failure.

The question therefore arises whether the evidence of the electrocardiograph improves upon the clinical evidence in making a prognosis. In particular, it may be asked: is the prognosis worse in the patient with an abnormal E.C.G. than in the patient with a normal E.C.G., when both develop pain in the same circumstances? And does the nature of the E.C.G. abnormality affect the prognosis in patients with similar pain? There does not appear to be sufficient information, either in the paper by Block et al. or in other sources, to answer these questions satisfactorily.

INDETERMINATE ATTACKS OF CHEST PAIN

Patients may complain of recurrent attacks of precordial pain or discomfort which is not related consistently to effort and does not definitely suggest any other recognised syndrome. Some such patients are of low intelligence; some have so convinced themselves that their symptoms are due to "wind" or "indigestion" that it is wellnigh impossible to differentiate between their actual sensation and their own interpretation of it; and others apparently have recurrent attacks of pain which suggest the likelihood of coronary-artery disease but are not brought on by effort.

Since the patients in this group are heterogeneous, it is difficult to make sound generalisations as to the value of the E.C.G. in their elucidation. An abnormal E.C.G. undoubtedly favours the hypothesis that the symptoms are due to coronary-artery disease. On the other hand, it is not very unlikely that coronary-artery disease with consequent E.C.G. abnormalities will occur in the patient whose symptoms have another cause. The E.C.G. may be of particular value when there are repeated minor episodes of cardiac infarction. The clinical picture may then be obscure, since the recurrent pain does not correspond to angina of effort and there are no general disturbances suggesting infarction. Here, the changes in a series of E.C.G.s may be diagnostic, though a normal E.C.G. does exclude repeated minor infarction.

Among the other definite disease processes which may cause recurrent chest pain of an indeterminate nature are œsophagitis or œsophageal ulcer and mediastinal involvement by bronchial neoplasm and other conditions. The E.C.G. is of no help in discovering these disorders, except in that a normal tracing may suggest that their possible presence should be considered.

EMOTIONAL CARDIOVASCULAR SYMPTOMS?

The cardiovascular symptoms which are often emotional include palpitation and awareness of "rapid beating of the heart" feelings of dizziness and faintness, and sighing respirations. They are typically associated with other manifestations of emotional disturbance such as tenseness, worrying over trivialities, sweating, trembling, exhaustion, and insomnia. Pain may accompany these symptoms. Its

quality varies widely, but it is often felt in the region of the apex of the heart and may be of a " dragging ", " aching ", or " stabbing " character. It is not regularly brought on by exertion or quickly relieved by rest.

Many patients with pain of this kind have been wrongly held to have angina of effort. The prime means of avoiding this error are, firstly, a careful analysis of the pain and, secondly, study of the patient as a whole, with all his other symptoms. The E.C.G. is valueless. In general the patient with emotional cardiac symptoms has a normal E.C.G., but this is not always so. The introspective man who has a cardiac infarct and is kept in bed for a long spell and is then ordered a tedious convalescence is apt to suffer profound psychological trauma, and is therefore unduly liable to emotional cardiac symptoms. His E.C.G. may be definitely abnormal, and the observer who concentrates his whole attention on the tracings and is incapable of seeing the patient as a whole may reach the wrong conclusion that he has angina of effort. On the other hand, to deduce that a patient cannot have angina of effort because a 12-lead E.C.G., even after exertion, is quite normal, and that therefore he must be neurotic, is an example of the deplorable practice of diagnosing neurosis by excluding organic disease.

SUSPECTED CARDIAC INFARCTION

The clinical picture of cardiac infarction is sometimes characteristic. If a patient with the typical story of angina of effort is suddenly seized with pain of the usual distribution while at rest, which persists for hours and is accompanied by sweating, it is in the highest degree likely that he has had a cardiac infarct. On the other hand, one of the commonest problems of medicine is the patient with a sudden illness which may be due to a cardiac infarction but may be due to something else. Among the reasons for the confusion are that some cardiac infarcts are not accompanied by pain, or cause pain in unusual sites such as the back or abdomen, and that certain other disasters may give rise to symptoms similar to those of cardiac infarction. These other disasters include pulmonary embolism, dissecting aortic aneurysm, pericarditis, and perhaps perforated peptic ulcer or acute pancreatitis.

Here, the E.C.G. is of undoubted value. The positive finding of the characteristic E.C.G. changes of recent cardiac infarction will make that diagnosis virtually certain.

From an analysis of 266 postmortem records of a consecutive series of patients found to have died from myocardial infarction, or suspected of dying from this cause, in the Royal Infirmary, Edinburgh, during the years 1954 and 1955 Paton (1957) reaches the following conclusions.

1. Only 44% of myocardial infarcts revealed at necropsy were diagnosed clinically.

2. The electrocardiographic diagnosis of recent myocardial infarction is very accurate. Only 6 incorrect diagnoses were made in 97 cases, and 3 of these 6 revealed bundle branch block (which is known to mask the changes of infarction).

3. Among the 37 patients who did not die suddenly but were diagnosed as having myocardial infarction without electrocardiographic confirmation, the diagnosis was correct in 13 cases and incorrect in 24 cases.

To suggest that because the E.C.G. evidence is superior to the clinical evidence in these fatal cases, the same is necessarily true of non-fatal cases is quite unjustified. The clinical picture of massive myocardial infarction is often very similar to that of, say, massive pulmonary embolism; in both circumstances the patient is usually shocked, dyspnœic, and desperately ill. The clinical pictures of minor myocardial infarction and minor pulmonary embolism are usually very different. Moreover, Paton's series contains a large proportion of patients who had had operations, which makes the clinical diagnosis of superadded myocardial infarction much more difficult.

In particular, it does not follow that because fatal myocardial infarction nearly always causes characteristic E.C.G. changes, the same is true of non-fatal infarction. Yet such statements as the following (*Lancet*, editorial, 1958) are now frequently made:

" Electrocardiography is an extremely accurate guide in the diagnosis of myocardial infarction, and it is now usually agreed that a 12-lead electrocardiogram does not remain normal after acute infarction: in case of doubt it should be repeated."

It is to be hoped that this is not " usually agreed ", since it is quite insusceptible of proof. Manifestly, there is no way of proving that a patient has not had a non-fatal cardiac infarction. There is also much suggestive evidence against the belief that a 12-lead electrocardiogram never remains normal after acute infarction.

Thus, it cannot be disputed that the E.C.G. changes may be slight or absent at first, only appearing in subsequent tracings. This certainly suggests that a small infarct, or an infarct in certain parts of the myocardium, may never produce E.C.G. abnormalities.

There is also the important complication that the shape of the E.C.G. tracing before the suspected cardiac infarction is rarely known and may well have been already abnormal; so we cannot know precisely what changes have followed the recent incident.

The serum glutamic-oxalacetic-transaminase (S.G.O.T.) level is now used as an index of myocardial infarction. It has been shown by Keele et al. (1958) and by other writers that some patients whose E.C.G.s remain normal have a raised S.G.O.T. level. This is certain proof that either the E.C.G. or the S.G.O.T. is an imperfect index of myocardial infarction.

When the question at issue is whether or not a patient has had a cardiac infarct of moderate severity, an E.C.G. which confirms this diagnosis may be of great practical value. And the erroneous diagnosis of a perforated peptic ulcer or other acute abdominal emergency, when the patient in fact has had a cardiac infarct, has grave consequences, though this error is rare. But when the question at issue is whether or not a desperately ill patient's disaster is a cardiac infarct—and here mistakes made from the clinical picture are common—correct diagnosis matters comparatively little. Most of such patients die, and the initial treatment is little affected by the diagnosis, consisting in general measures to combat shock and anoxæmia.

A common problem is the decision whether or not a patient has had a minor cardiac infarct (and here a normal E.C.G. does not exclude an infarct). The general practitioner often sees patients who have had a brief attack of precordial pain. Many people with such pain attribute it to " wind " or " indigestion ", never visit their doctors and, after the pain has ceased, carry on with their usual activities. Undoubtedly, very large numbers of minor infarcts are not diagnosed at the time. Routine postmortem studies on patients who have died for non-cardiac reasons frequently reveal scars which suggest old infarcts.

This decision whether or not a patient has had a minor infarct is widely thought to be important; the strenuous efforts to find an E.C.G. abnormality by taking repeated multi-lead tracings confirm that this is so. But there is no clear evidence that harm results if a minor infarct is not diagnosed. In a situation such as this the only means of obtaining useful evidence would be a large carefully controlled series, half of whom were given the approved treatment, and the other half allowed to go about their usual business. (And the very minor cases would tend not to be included in such a series, since many of them would not reveal unequivocal E.C.G. evidence of cardiac infarction.) The problem must therefore be considered a priori. Those who say that to miss a minor cardiac infarct is serious would presumably argue that the damaged heart would suffer by being subjected to continued " strain ", but would be enabled to recover by the patient's resting for some weeks. The best grounds for viewing such reasoning with suspicion is to remember that bleeding, purging and starving, prolonged bed rest after operations, and innumerable other happily extinct procedures all depended, not on evidence that they worked, but on a-priori speculation.

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Electrocardiography gives information about the site and extent of infarcts. Knowledge of the site matters little; knowledge of their severity is important in assessing prognosis and possibly in giving guidance about treatment. In general, the greater the E.C.G. abnormalities, the more extensive is the infarct. The question therefore arises whether the information given by the E.C.G. adds to that given in other ways. The outlook is poor when the patient is initially shocked with a feeble pulse, or later develops congestive failure. And the patient whose pain is transient and is free of all other symptoms nearly always makes a good recovery. There appears to be no good evidence that the E.C.G. findings can legitimately modify the opinion of the severity of the process which has been reached on clinical grounds.

Routine Electrocardiography

Except for research purposes, electrocardiography on the apparently healthy is rarely carried out in Britain. According to many reports the situation is very different in America. There, vast numbers of " busy executives " have their regular E.C.G. among other numerous routine investigations, and vast numbers of ordinary employees have an E.C.G. among other procedures before they are given a job. Accounts of some of the consequences of this routine electrocardiography make sombre reading.

Sprague (1948) even says that on his advice certain men are retired from work solely on account of marked E.C.G. abnormalities such as inverted T_1 and bundle branch block. Compulsory retirement is no doubt uncommon, but compulsory transfer to other work and rejection from employment purely or largely on E.C.G. grounds appear to be common. There is good evidence that certain E.C.G. abnormalities alone indicate that the subject has an expectation of life below average. A firm can therefore argue that such a man is unlikely to give long service, will be unduly liable to be absent from work, and will upset the financial aspects of the pensions scheme. But if all other firms advance the same argument nobody will employ him. This is not only a monstrous injustice to the unfortunate victim: in addition, he will become a charge on the community.

It is arguable that some men should be *advised* not to do certain kinds of work on medical (including electrocardiographic) grounds, though circumstances in which there is convincing evidence to support this argument are rare indeed. But to *compel* them not to do such work (except when there is a risk that others may suffer, as when a bus-driver is thought to be liable to cardiac infarction) is a serious interference with the liberty of the subject. Doctors should take no part in this compulsion.

In an article on " the electrocardiogram in the examination of the industrial worker " Durham and McGee (1954) say that this " can benefit the individual employee by uncovering disease in an early and possibly remediable stage ". Unfortunately, no examples are given of this kind of benefit. In fact, it is difficult to conceive how the future health of people with E.C.G. abnormalities which are found in this way will be improved by so-called treatment. On the other hand, if a man is told that he has an abnormality he may be worried, and if he is given " treatment " (which will probably consist of advice to cease various activities or to live very quietly) there is all the more likelihood that he will be worried.

It can be argued that a normal routine electrocardiogram is reassuring to the subject who has been worried about his heart. Durham and McGee say " the tracing *per se* unquestionably impresses the average worker. It assures him that he has been examined ". No doubt this is true. Many lay people, and also, it is to be feared, some medical men, take it for granted that an elaborate bit of machinery such as the electrocardiograph will reveal the truth. A normal E.C.G. is no proof that the heart is normal. And the best evidence that a heart is functioning well is the absence of symptoms.

Accuracy of E.C.G. Reports

It has been assumed so far in this paper that an E.C.G. is either normal or abnormal. In practice it may be difficult or impossible to decide into which of these categories an E.C.G. should be placed. Davies (1958) has produced much interesting information on this matter.

He submitted 100 E.C.G.s to 10 observers (9 of whom were experienced cardiologists) who were asked to make one of the following three reports on each: normal, infarction, or abnormal (covering all heart-diseases except infarction). The same 100 E.C.G.s were again reported on by the same observers after an interval. Clinical details were not given.

Complete agreement between all observers was reached in one-third of the 100 tracings and majority agreement in half. There was considerable dispute about one-fifth of the tracings. After the second reading each observer on average disagreed with one in 8 of his original reports. This observer variation affected the normal, abnormal, and infarction tracings equally.

Davies reaches this wise conclusion:

" From the standpoint of electrocardiographic diagnosis it is an illusion to believe that there can be any arbitrary line between normal and abnormal tracings or between abnormal and infarction tracings. The ranges of each overlap and do so more widely than is generally realised. . . . It is apparent that tracings from the intermediate zones are of little or no diagnostic value, but are very likely to be interpreted according to the clinical bias. In this way observer variation may add to diagnostic error . . ."

This statement is a particular example of the general proposition that minor deviations from the average are of negligible value in diagnosis. Those subtle physical signs such as an increased area of cardiac or splenic dullness to percussion or slight pallor of the temporal half of the optic disc, and minor X-ray findings such as tiny shadows on the chest film or " spasm " of the duodenal cap only lead to diagnostic errors. In broad, the useful physical signs or findings of investigation are those about which all observers are agreed; if there is disagreement the reality of the finding should be suspect.

It has been argued that the situation in real life is not so bad as that suggested by Davies' experiment because the observers were only allowed to make one of three diagnoses (and in particular could not report " doubtful ") and because no clinical details were given. This is sound criticism as regards the limitation of diagnoses but not as regards the absence of clinical details. The statement that an opinion on a patient should not be made solely from the E.C.G. but should always be made from a consideration of all available information is supremely correct. It is another thing to assert that the opinion on an E.C.G. should not be made without knowledge of the patient. On the contrary, the report would in general be more dependable without that knowledge than with it. If the observer knows, for example, that a patient has had an attack of precordial pain suggesting cardiac infarction it becomes easy to give spurious support to that diagnosis by noticing minor deviations from the average in the E.C.G. which would otherwise have been rightly ignored.

Reasons Why E.C.G. is Overvalued

The above considerations suggest that electrocardiography has been greatly overvalued in the investigation of patients with suspected coronary-artery disease. There are two main reasons for this overvaluation.

Nature of Coronary-artery Disease

Coronary-artery disease varies infinitely in its course and severity and in lesser degrees is extremely common among the middle-aged and old. In only a tiny minority of cases does it cause an acute fatal illness, but this tiny minority has to an excessive degree coloured the picture of the disease, because only they are subjected to histological study. To draw deductions about the minor cases from the few fatal cases is quite improper. In truth, although we can rightly deduce that if a subject can perform hard physical exertion without distress his coronary circulation must be efficient, there are no means of knowing what is the extent of the coronary sclerosis or of myocardial damage in the majority of people. There is therefore no check on the information given by the E.C.G., which in consequence becomes overvalued. The unjustified belief that a normal E.C.G. excludes cardiac infarction could only arise because means of reaching the truth do not exist.

Investigations which are concerned with progressive diseases do not become overvalued in this way. No-one would be so foolish as to claim that a normal barium meal can exclude carcinoma of the stomach, a normal electroencephalogram can exclude a glioma, or a normal spine X-ray can exclude secondary deposits.

Because fatal and severe coronary-artery disease are undeniably important people tend to assume the importance of determining whether or not a patient has minor coronary-artery disease. In practice this matters comparatively little. The presence of such disease neither provides a good reason for giving treatment nor enables an accurate prognosis to be made. Because the importance of the problem is exaggerated, the importance of the means which is thought to solve it—electrocardiography—is exaggerated in turn.

The Fascination of Machines *

Among all the machines used for diagnosis, perhaps the electrocardiograph is the most impressive. When the general practitioner wants to know the answer to the question: " is it a coronary ?" and calls in the cardiologist on a domiciliary visit, the patient may easily believe that an almost magical performance is taking place, as the specialist peers at the gleaming white box, adjusts the switches, and studies the record as it pours out. It is to be feared that many doctors, and even cardiologists, are in their heart of hearts also so impressed as to take it for granted that the machine reveals the truth. In addition, the electrical basis of electrocardiography is so complicated that few understand it.

A *Lancet* editorial (1958) in discussing the use of electrocardiography in diagnosing cardiac infarction concludes: " Here at least must we admit that machines are far less fallible than man ". This sentence seems to imply that the machine gives its answers quite independently of man. In fact, the readings given by the machine are only useful when interpreted by man; and this interpretation is not always simple. Moreover, even if in this particular situation the electrocardiographic evidence alone is superior to the other evidence alone, in practice all the available evidence should be considered together. The antithesis between the machine and man is therefore false, not only because the two are not equivalent but also because the machine should be the servant of the man.

* This phrase is borrowed from Pickering (1955).

Summary and Conclusions

1. Electrocardiography cannot help in deciding whether or not a patient has angina of effort. It is of small or doubtful value in determining both ætiology and prognosis when angina is present.

2. When a patient gives a history of attacks of precordial pain of an indeterminate character, electrocardiography is sometimes of considerable help.

3. In differentiating between emotional cardiac symptoms and angina of effort the electrocardiograph is valueless.

4. When cardiac infarction is suspect, electrocardiography gives unequivocal guidance if the characteristic E.C.G. changes of recent infarction are present. But the E.C.G. only imperfectly reflects the gravity and extent of the process in the heart, and a normal E.C.G. cannot exclude infarction.

5. Used routinely, electrocardiography may enable insurance companies to refuse to insure a life, or enable employers to refuse someone employment. It is useless to the individual concerned, and by bringing to light minor abnormalities may make it possible for an unwise physician to turn him into an invalid.

6. The interpretation of E.C.G.s is often difficult, there being great variation between the reports of different experts on the same tracing, and considerable variation in the reports of the same expert on the same tracing at different times.

7. The reasons for the overvaluation of electrocardiography are discussed.

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VITAMIN B_{12} AND THE COURSE OF DIABETIC RETINOPATHY

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As Wagener (1945) points out, the increased incidence of retinopathy is probably due to the longer survival of the diabetic which has followed the introduction of insulin. In recent years, improved histological techniques have revealed characteristic vascular changes in the diabetic's retina (Ballantyne 1946, Ashton 1949), but the causes of these remain obscure. The ætiological roles of the pituitary and adrenal glands (Becker 1952, Poulsen 1953, Kinsell et al. 1954), fats (Iannaccone and Kornerup 1954, Cook 1957), and mucopolysaccharides (Gilliland 1954, Adlersberg et al. 1956) have still to be decided.

An abnormality of vitamin B_{12} metabolism in diabetics was first suggested by Becker et al. (1953). They found that in patients with retinopathy the urinary excretion of an injected dose of vitamin B_{12} was abnormally high, but that in diabetics without retinopathy excretion was subnormal. Furthermore, using rabbits made diabetic with alloxan, Becker et al. (1954) produced capillary changes in the retina by giving corticotrophin and depleting the animals of B_{12}.

Though occasional reports and references to the use of vitamin B_{12} in the treatment of diabetic retinopathy have appeared (Sancetta et al. 1951, Becker et al. 1953, Friedenwald 1953, 1954, Gurling 1955, Lederer et al. 1955, Forster 1956), none is a valid assessment of a therapeutic agent (Pickering 1949, Bradford Hill 1951). A controlled clinical trial of vitamin B_{12} was therefore undertaken. This revealed interesting new information about the course of diabetic retinopathy.

Material and Methods

25 diabetic patients with mild retinopathy were selected from the diabetic clinic at St. Mary's Hospital. Mild retinopathy was defined as the presence only of the dotlike so-called microaneurysms, with or without a few hæmorrhages and exudates. Patients of both sexes were included, and an attempt was made to cover a wide age range and to include insulin-treated and diet-treated cases.

Candidates for the trial were seen at a special assessment clinic where both fundi were examined after full dilatation of the pupils. A patient admitted to the trial was paired with another of the same sex and age ($\pm$2·5 years), duration of diabetes ($\pm$2·5 years), and diabetic treatment category. A member of each pair was given 50 μg. vitamin B_{12} by mouth three times a day for the trial period; the other member took exactly similar but inert tablets. The allocation of active and inert tablets to each member had been randomly determined by a colleague, and was unknown by the observer or the patient.

A segment of one retina containing lesions was then selected for study; it was usually bounded by identifiable anatomical limits, and often totally enclosed by retinal vessels. The limits of the segment were accurately drawn (fig. 1) and six carbon copies were made. The extent of the segment was assessed approximately in "disc areas" and the lesions lying within it were accurately plotted on the first "map". Patients returned for reexamination at eight-weeklyintervals for about forty-eight weeks; at each visit the pupil was fully dilated, and the lesions present in the selected area were checked against previous records and recorded on a blank carbon copy of the original "map".

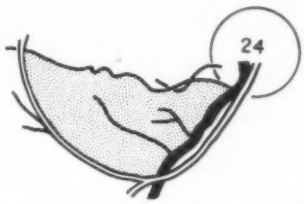


Fig. 1—The drawing of a segment selected for study (case 24).

At the end of the trial, three numerical assessments, "density", "change", and "activity" were calculated for each patient.

Density was derived by dividing the number of lesions at the first examination by the area of the segment.

Change was the difference between the number of lesions at the last and the first examinations, again divided by the segment-area. When the trial period was not exactly forty-eight weeks, a suitable adjustment was made.

Activity expresses the considerable coming and going of lesions in the segment from examination to examination. It is the sum of those lesions which disappeared and those which appeared at each examination in the trial period. This sum, divided by the segment-area, was adjusted if fewer than six reexaminations had been made.

These three factors were calculated for microaneurysms, hæmorrhages, and exudates separately, and for all together.

In 7 patients, absorption of orally administered vitamin B_{12} was proved by the method described by Schilling (1953). 0·5 μg. of vitamin B_{12} labelled with 1 μC of ^{58}Co was given by mouth and followed by a 1 mg. intramuscular "flushing" dose of unlabelled vitamin. Urinary excretion of radioactivity over the next twenty-four hours was measured, and expressed as a proportion of the dose administered. Apart from one low value, the proportions excreted fell well within the limits recorded by Schilling et al. (1955) (table I).

TABLE I—24-HOUR URINARY EXCRETION OF ^{58}Co-LABELLED VITAMIN B_{12} (1 μC ^{58}Co in 0·5 μg. vitamin B_{12} by mouth)

Patient	% dose excreted ±S.E.	
1	10·6	0·3
2	3·6	0·25
24	10·7	0·3
25	11·4	0·3
27	15·1	0·3
29	12·2	0·3
32	19·7	0·3

Results

Tables II and III show the mean values for "change" and "activity" in the 12 vitamin-treated and the 13 control cases. These values have been calculated separately for each type of lesion and for all grouped together. The probability values indicate that all the differences between the means could easily have arisen by chance.

When the compositions of the treated and control groups were compared in respect of other features, they were found to be closely similar in "density" of lesions; in the general eye appearance; in the effectiveness of diabetic control; and in the presence of other diabetic complications. Only the blood-pressure levels (measured once under standard conditions during the trial period) were found to differ considerably.

* Working as a Lund research fellow of the British Diabetic Association.

TABLE II—" CHANGE " IN B_{12}-TREATED AND CONTROL GROUPS
(Means ± S.E.)

—		Ma	Hb	Ex	All
Treated group	12	0·350 ± 0·37	−0·108 ± 0·48	0·060 ± 0·09	0·303 ± 0·54
Control group	13	−0·397 ± 0·33	−0·014 ± 0·13	0·379 ± 0·30	−0·032 ± 0·51
Difference		0·747	0·094	0·319	0·335
't'		1·51	0·19	0·97	0·36
P		<0·2	<0·9	<0·4	<0·8

For further analysis, the blood-pressure scores adjusted for age and sex were calculated for each patient by the method described by Hamilton et al. (1954). The resulting figure (representing the amount by which an individual pressure deviates from the mean of a " normal " group of the same age and sex, scaled to a comparable deviation at a standard age), enables one to compare directly the blood-pressures of subjects of differing age and sex. The mean age- and sex-adjusted score of the treated group exceeded that of the control group by 24·1 mm. Hg systolic, and 10·7 mm. Hg diastolic (table IV). Although calculation reveals a significant correlation between " change " of microaneurysms and the systolic age-adjusted score ($r = 0·44$, $P < 0·05$), the difference of 24·1 mm. Hg is not adequate to have masked an effect of vitamin B_{12} in the comparison shown in table II.

TABLE III—" ACTIVITY " IN B_{12}-TREATED AND CONTROL GROUPS
(Means ± S.E.)

—		Ma	Hb	Ex	All
Treated group	12	6·523 ± 1·27	3·417 ± 1·07	0·628 ± 0·27	10·567 ± 1·47
Control group	13	6·403 ± 1·78	1·862 ± 0·59	0·948 ± 0·37	9·215 ± 2·19
Difference		0·120	1·555	0·320	1·352
't'		0·13	1·30	0·68	0·50
P		<0·9	<0·3	<0·5	<0·7

The striking outcome of this study is the unsuspected degree of activity which repeated examination of the segment revealed. Study of the segment maps shows this activity in *all* the three elements recorded. Representative examples are depicted in figs. 2, 3, and 4. The range of "activity", calculated as described, is shown in frequency-distribution diagrams (fig. 5).

Between examinations hæmorrhages sometimes disappeared completely or gave place to exudate which might then disappear. Exudate was found in previously normal areas, and sometimes appeared around a microaneurysm. Its disappearance could be rapid and complete. The behaviour of the dot " microaneurysms " was more puzzling and unpredictable. These lesions appeared and disappeared with great frequency, and without visible intermediate changes (fig. 3). Some, however, remained quite unchanged through the period of observation. The appearance of a small fresh " blot " hæmorrhage at the site of a previously recorded microaneurysm was quite common, while, less frequently, an exudate might similarly appear. A feature worthy of special note was the disappearance of a microaneurysm from an easily identified site for one or two examinations, only to be seen again in an apparently identical situation, weeks or months later (fig. 4).

Discussion

Sources of Error

Quantitative assessment of diabetic retinopathy offers considerable advantages in evaluating a therapeutic agent, but before conclusions based upon it can be reached, certain sources of error must be considered.

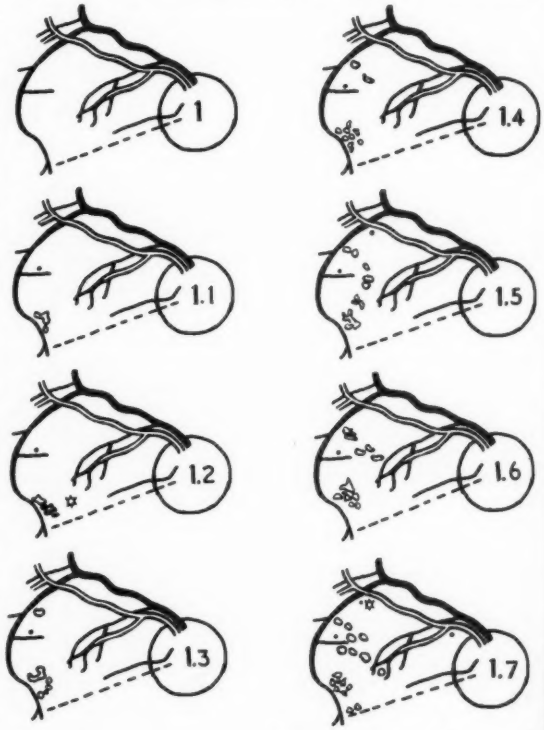
Observer error in medicine has received much attention (*Lancet* 1954, Hamilton 1958). We have made a special study of the size of this variation in the assessment of diabetic retinopathy, and the results will be published separately; the study showed clearly that the variation between two observers—and among multiple observations by the same observer—is small when individual lesions are mapped in a defined area, but large when a descriptive overall classification of changes is attempted.

An attempt to reduce observer error was made in the present study by referring to previous drawings each time a segment was reexamined. This might have resulted in a fictitious increase in the lesions, as those previously present and accidentally missed were noted. It also introduced an opportunity for bias in deciding whether a lesion was new or a previously recorded one. It is likely that such errors would be very small, and in any case would apply equally to treated and control groups.

TABLE IV—AGE- AND SEX-ADJUSTED BLOOD-PRESSURE SCORES IN B_{12}-TREATED AND CONTROL GROUPS
(Means ± S.E.)

—		Systolic " score "	Diastolic " score "
Treated group	12	23·75 ± 7·31	4·58 ± 4·74
Control group	13	−0·38 ± 4·40	−6·15 ± 6·15
Difference		24·13	10·73
't'		2·50	1·36
P		<0·05	<0·2

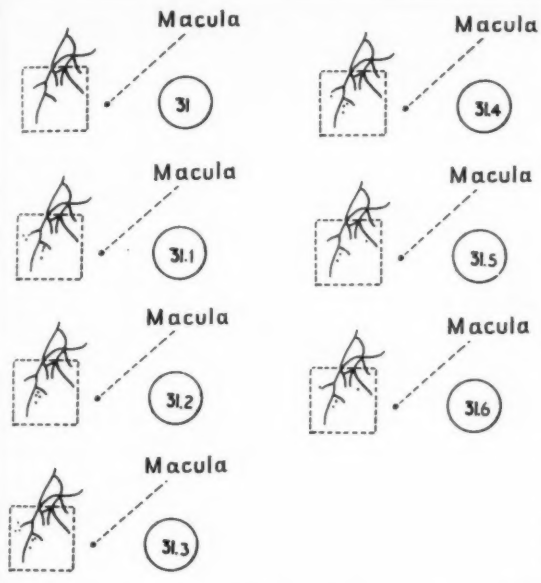
The numerical assessment of lesions described above is not without objection. While it is not difficult to count discrete lesions such as microaneurysms, it is less easy to decide on the



Case 1	Ma	Hb	Ex	All
Activity	1·33	1·00	3·33	5·67
Density	0·33	0·00	0·67	1·00
Change	0·66	0·33	3·33	4·33

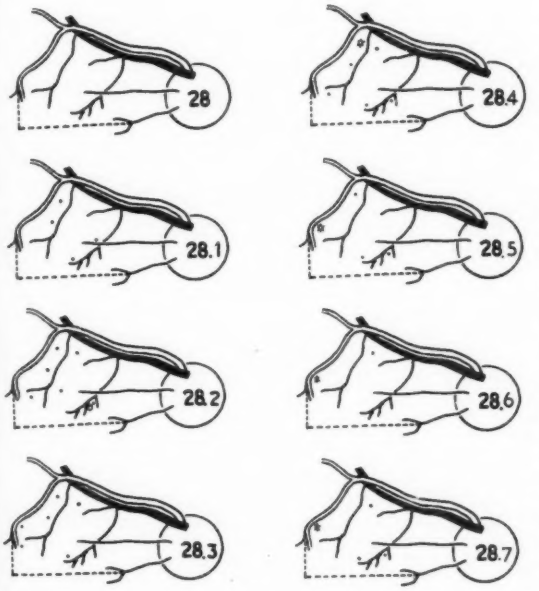
Fig. 2—A complete 48-week record.

Microaneurysms (Ma) are shown as dots, exudates (Ex) as demarcated white areas, and hæmorrhages (Hb) as white areas with radiating " legs ". The record shows a progressive accumulation of exudate with a microaneurysm making a brief appearance at the upper angle in map 1·5.



Case 31	Ma	Hb	Ex	All
Activity	15·60	0·00	0·00	15·60
Density	5·00	0·00	0·00	5·00
Change	—1·00	0·00	0·00	—1·00

Fig. 3—The considerable variability in the appearance of microaneurysms is evident in this record.



Case 28	Ma	Hb	Ex	All
Activity	10·08	1·44	0·96	12·48
Density	1·60	0·00	0·00	1·60
Change	—0·42	0·42	0·00	0·00

Fig. 4—The dynamic nature of diabetic retinopathy.

Just below the centre of the segment, a diagonally running vessel gives off three short branches. In the angle between the first of these and the parent vessel, a microaneurysm can be seen in maps 28·2, 28·4, 28·5 and 28·7; it is not visible, however, in maps 28·1, 28·3 and 28·6. Hæmorrhage from, and disappearance of, another microaneurysm can be seen at the upper angle of the area.

"score" for a lesion of changing size, such as an exudate. Thus the appearance of a new lesion scores the same as the enlargement of an existing one, but how comparable are the two events? A similar problem arises in the following circumstances. A lesion identified as a microaneurysm later ruptures giving rise to a hæmorrhage. This then gives place to an exudate, which in its turn disappears completely. When this is numerically assessed, it gives the same value as if in one area of the segment a preexisting microaneurysm had disappeared; in another, hæmorrhage appeared, later to clear; and in yet another, an exudate came and went. In the first case the "score" represents what is probably the natural history of a single lesion, while in the second the same value represents three separate events occurring in different parts of the segment. Error is also introduced if a previously recorded lesion escapes notice, for it is then registered as disappearing. If it is identified at a later examination, it is scored as a new lesion, thus erroneously counting twice in the assessment of "activity". Further, as has been shown, a microaneurysm may be invisible at some examinations and visible at others, and will then score the same as if completely new microaneurysms were coming and going at different sites.

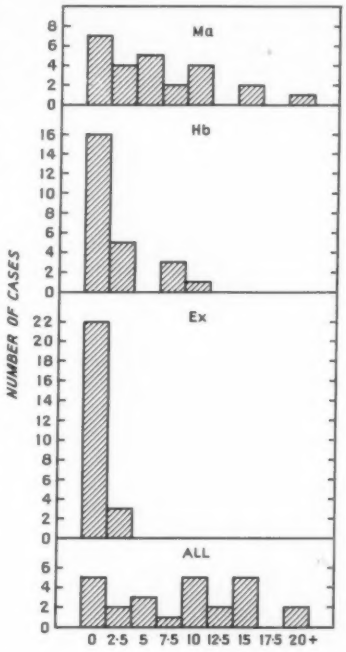


Fig. 5—Frequency distribution histogram of range of "Activity" in microaneurysms (Ma), hæmorrhages (Hb), exudates (Ex) and all lesions together (All).

The vertical axis indicates the number of cases, and the horizontal axis, "Activity".

The identification of individual lesions occasionally presents difficulty, particularly in distinguishing between microaneurysms and small hæmorrhages. When in doubt, we have classified a lesion as a hæmorrhage rather than a microaneurysm, and we did not reclassify lesions on the basis of their subsequent behaviour. We have assumed that the small, regularly round, dark-red dots—so characteristic of diabetic retinopathy, and included in the terms "deep or punctate hæmorrhages" in earlier descriptions (Duke-Elder 1945)—are in fact microaneurysms. Many of the lesions revealed by injection studies of the retinal vessels (Ashton 1949), measuring up to 100 μ in diameter, are well within the limits of resolution of the clinical ophthalmoscope. Cordes (1952) believed that all so-called punctate hæmorrhages were microaneurysms, while Ballantyne and Loewenstein (1944) thought that many were, and demonstrated them by microdissection. Lesions which we recorded as microaneurysms varied considerably in size, and, although some could be seen quite readily, others were small and required careful search. This was the main reason for our decision to refer back to previous records at each new examination.

Finally, we must emphasise that our observations apply to ophthalmoscopically visible lesions only. We are unable to say how well their behaviour represents that of the many hundreds of unseen lesions which injection studies disclose.

Although these criticisms and comments are applicable to both treated and control groups in this study, and thus "cancel out" in the assessment of the effects of treatment, they are important when general conclusions about the behaviour of diabetic retinopathy are drawn from the observations.

Role of Vitamin B_{12} in Diabetic Retinopathy

Becker et al. (1954) base their case for a disorder of vitamin-B_{12} metabolism in diabetics upon their demonstration that, by comparison with normal urinary excretion of about 20% of a 50 μg. dose given by injection, patients with retinopathy excreted about 40%, and those without retinopathy about 8%.

The increased loss in patients with retinopathy could be reduced by administration of testosterone, an effect which they thought was mediated by suppression of pituitary-adrenal overactivity, and established their claim that coexistent renal disease was not responsible. Support came from the work of Stone and Chow (1957) who studied urinary excretion of radioactive cobalt-labelled B_{12} given by mouth, using the method of Schilling (1953). Their group of uncomplicated diabetics excreted only 6·64% of the 2 μg. dose while those with retinopathy and non-diabetics excreted 10·86% and 10·80% respectively. Studies of the fæces of the uncomplicated diabetics suggested diminished absorption from the intestine. This finding does not, however, justify their assumption that the cases with retinopathy were also underabsorbing and, relative to the non-diabetics, overexcreting. Bookman et al. (1957), Field et al. (1957), and Boger et al. (1958) have failed to find any relationship between B_{12} excretion and retinopathy.

The retinal lesions produced in alloxan-diabetic rabbits by corticotrophin administration and vitamin-B_{12} depletion are quite unlike those of human diabetic retinopathy in form. The interpretation of such appearances is further confused by the capillary looping and irregularity found in the normal rabbit retina (Ashton 1958). In the face of this and the failure of other workers to produce capillary changes using similar methods (Marble 1954), it was not surprising—though a little disappointing—when Becker's group later withdrew their claim (Rosen et al. 1954).

It may be argued that we selected the wrong type of retinopathy to demonstrate an effect of vitamin B_{12}, but reports of its use (Sancetta et al. 1951, Becker et al. 1953, Lederer et al. 1955, Friedenwald 1953, 1954) do not specify the type in which it is specially beneficial; in any event, there was no indication of an effect in any of the three classes of lesions studied by us.

At present, the balance of evidence is against a fundamental role for vitamin B_{12} in the pathogenesis of diabetic retinopathy, but suggests that disturbance in its metabolism may be an associated phenomenon.

Course of Diabetic Retinopathy

The literature of diabetic retinopathy abounds with references to the changeable ophthalmoscopic picture (O'Brien and Allen 1942, Lawrence 1949, Peck et al. 1949, Whittington 1951, Becker et al. 1954, Gurling 1955). Our observations suggest that the pathological process is much more dynamic than is usually thought.

While changes in hæmorrhages and exudates can be explained by known pathological mechanisms, variation in behaviour of the microaneurysms is less readily understood. The disappearance of such lesions and their reappearance in an identical situation raises the question of the factors which govern their visibility. The chief of these must be the blood-flow through the thin-walled sac, and this depends upon intracapillary pressure, and its relationship with retinal-tissue tension and intraocular pressure. The importance of retinal swelling upon the blood-flow through vessels in the kitten's retina has been strikingly demonstrated by Ashton et al. (1953, 1954, 1957). Variation in the levels of blood-sugar changes the intraocular pressure (Poos 1930), and Poulsen (1958) has influenced the size of microaneurysms by inducing hypo- and hyper-glycæmia in diabetics. The apparently beneficial effects of hypophysectomy upon the progress of diabetic retinopathy may in part be due to the considerable falls in blood-pressure which occur postoperatively (Luft et al. 1955). The few attempts which we have made to lower pressure in the ophthalmic artery, by digital compression of the common carotid, have not led to any striking immediate change in the ophthalmoscopic appearance.

Consideration of the basic process of capillary proliferation and looping (Ashton 1953) suggests that microaneurysm formation is potentially reversible. If any of the variability in appearance which we witnessed does, in fact, represent resolution and formation of lesions, then the small net change over the course of a year indicates that the balance between the two processes must be fairly even; a disturbance of the equilibrium could lead to rapid worsening or improvement in the ophthalmoscopic appearance. Clinical factors which might influence this equilibrium are being examined in the group as a whole and will form the basis of another report.

Conclusions

This study has failed to show an effect of vitamin B_{12} given by mouth upon the course of diabetic retinopathy. It has, however, emphasised the value of a method focusing attention upon the fate of individual lesions in a well-demarcated segment of the retina. Not only does this method give a valid assessment of a therapeutic effect, but it also promises to provide new knowledge of the natural history of diabetic retinopathy and its pathogenesis.

Summary

In 25 diabetic patients with early retinopathy, individual lesions in a selected segment of the retina have been followed for a year.

150 μg. vitamin B_{12} daily, given by mouth to 12 of the patients gave them no advantage over the 13 controls.

The dynamic nature of the lesions is evident. In its early stages, the pathological process is probably reversible.

We wish to thank Messrs. Glaxo for supplying the B_{12} and placebo tablets; Dr. M. Hulbert, department of radiotherapy, St. Mary's Hospital for the ^{57}Co-B_{12} absorption studies; Dr. P. N. Cardew and staff, photographic department; Dr. C. A. Young, physician in charge of the diabetic clinic, St. Mary's Hospital; and the 25 patients.

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EFFECT OF DRUGS ON MOTION SICKNESS PRODUCED BY SHORT EXPOSURES TO ARTIFICIAL WAVES

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MANY drugs have been used to prevent motion sickness, but, whenever they have been objectively compared over periods of motion lasting about an hour, hyoscine hydrobromide in doses of 0·6–1·2 mg. has been found to be more effective than any other treatment (Holling et al. 1944, Hill and Guest 1945, Tyler 1946, Strickland et al. 1950, Glaser and Hervey 1951, 1952, Chinn et al. 1953).

In a series of experiments which were carried out on troopships and lasted several days at a time (Report 1956) meclozine hydrochloride (' Ancolan ', ' Bonamine ', ' Meclizine ', ' Postafene ') in doses of 50 mg. once or twice daily was found to be the most effective. The action of meclozine persists for more than twenty-four hours; and the design of these experiments favoured long-acting drugs, as the subjects were given the first dose of any treatment at the beginning of the journey and then at meal-times. Since the subjects got up some time before breakfast, drugs which had lost their effect overnight could give no protection on rising, when the incidence of sickness was likely to be highest (Tyler and Bard 1949). In the same trials cyclizine hydrochloride (' Marezine ', ' Marzine ') in doses of 50 mg. twice daily was also found effective. Neither meclozine nor cyclizine have been effectively compared with hyoscine over short periods of exposure, and it seemed necessary to do so, especially since many more people are exposed to wave motion for short periods than for long ones. Other mildly effective preventives, such as promethazine (' Phenergan ', ' Avomine ') or diphenhydramine (' Benadryl ', ' Dramamine ') had previously been tested against a dummy and hyoscine (Glaser and Hervey 1951, 1952, Chinn et al. 1953), but it seemed of interest now to extend the tests to the so-called " tranquillisers "; and perphenazine (' Trilafon ') seemed to be the one to try, because it had cured postoperative vomiting (Scurr and Robbie 1958).

Material and Methods

Subjects

77 soldiers, aged 19–25 years, from various military units had volunteered for these tests. Throughout the experiment they lived together near the experimental tank. On the day before the first test they were given a questionary asking them in randomised sequence about previous exposures to and experience of motion sickness. Samples of subjects may differ in their susceptibility to motion sickness, and it was of interest to know how the present subjects would compare with other groups of men. Table I shows that all kinds of past experience were included in the present sample; some men had had no experience of severe motion, others had experienced motion with or without motion sickness, while others had been sick on swings or in motorcars and were obviously highly susceptible. The present subjects were similar in this respect to soldiers tested before (Glaser and Hervey 1952), but a random sample of 66 male students of the same age-group had had more experience of severe motion and appeared to be more susceptible to motion sickness (table I). This will be further discussed below.

After the experiment had been explained to the soldiers, all agreed to take part in it; but in the first test 1 subject had to be discharged from the experiment as he developed slight tetany from excessive vomiting, and after the first test 3 subjects asked to return to their units for reasons not connected with the experiment. Two other subjects were unable to take part in the last two tests owing to minor accidents at games. The randomised experiment had been designed for 72 subjects, and sequences of treatment were picked at random for the extra 5 subjects. For this reason, the number receiving each treatment on one day varied from 12 to 14 (table II).

TABLE I—PREVIOUS EXPERIENCE OF MOTION SICKNESS IN THE EXPERIMENTAL SUBJECTS AND IN A GROUP OF STUDENTS

Previous experience of:	Experimental subjects (77 soldiers)	Control subjects (66 students)
Rough sea (%)	53	74
Seasickness (%)	33	74
Flying (%)	51	64
Airsickness (%)	5	23
Carsickness (%)	21	59
Sickness on swings (%) ..	26	35

Drugs, Dummies, and Controls

The drugs used were hyoscine hydrobromide 1 mg., cyclizine hydrochloride 50 mg., meclozine hydrochloride 25 mg., and perphenazine 8 mg. The dummies contained lactose 100 mg. In each test a sixth of the subjects received no treatment at all—not even a dummy. The dosage of hyoscine was chosen on the basis of previous experiments (Glaser and Hervey 1951, 1952), and that of the proprietary preparations on the advice of their makers. All drugs were white powders, and they were made up with lactose in gelatin capsules to a volume equivalent to lactose 100 mg., so that they were indistinguishable from each other and from the dummy.

Procedure

All six possible " treatments " were coded at random, and nobody concerned with the experiment knew the code to the capsules until all the results were calculated; while those computing the results knew neither the code to the capsules nor which was the untreated group. The capsules were issued in envelopes marked with the subject's number and the date. Each subject received each of the six treatments in turn, and in randomised sequence. In addition, in each of the last five tests each treatment was preceded by every other treatment a similar number of times. The subjects were distributed over six inflatable tented rubber floats so that every treatment was represented on each float a similar number of times in each test, but the position of each float in the experimental tank varied from test to test. While exposed to wave motion the subjects were asked to sit up in order to have constant and maximal stimulation of their vestibular apparatus (Tyler and Bard 1949), but they changed places every five minutes, so that any effect of their position in the float was randomly distributed. The floats were closed in, so that the subjects could not look out of them.

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TABLE II—INCIDENCE OF VOMITING AND NAUSEA AFTER VARIOUS TREATMENTS

Treatment	Test 1				Tests 1–3				Tests 1–6			
	No. treated	No. vomiting	No. feeling sick only	Total	No. treated	No. vomiting	No. feeling sick only	Total	No. treated	No. vomiting	No. feeling sick only	Total
None	14	14†	..	14	40	18	3	21‡	72	21	8	29
Dummy	13	5*	4	9	39	11	10	21‡	74	15	17	32
Hyoscine	14	3*	2	5	37	4	3	7§	73	4	6	10
Cyclizine	12	8*	2	10	34	8	3	11‡	73	9	9	18
Meclozine	12	6*	3	9	37	14	7	21‡	73	17	12	29
Perphenazine	12	7*	3	10	36	14	7	21‡	73	16	17	33

Numbers marked * are statistically compared in fig. 2 with the number marked †. Numbers marked ‡ are statistically compared in fig. 3 with the number marked §.

Tests were conducted at intervals of forty-eight hours, except over the weekend when the interval was seventy-two hours. On each of the six experimental days the subjects finished breakfast by 9 A.M. and remained indoors without further food until 12.40 P.M. when they were driven to the experimental tank which was 2 miles away. Just before 1 P.M. they sat down in a dining-room close to the experimental tank and at 1 P.M. they received their capsules, the observers (see below) making sure that capsules were received and swallowed. At 1.30 P.M. they had a standard lunch with unlimited water to drink, but no tea or coffee. Otherwise no attempt was made to control the intake of food, but the amount and quality of the food provided did not differ appreciably from day to day. Since it took twenty minutes to serve all meals, the order in which the meals were issued was varied. At 2.30 P.M. the subjects began to prepare for boarding the rafts and at 2.45 all the rafts were in position in the centre of the tank and the wave-making machine was started. For the next hour (from 1 hr. 45 min. to 2 hr. 45 min. after the capsules had been taken), the subjects were on the floats and exposed to motion. Thus the subjects were exposed to motion while all the drugs were at the peak of their action.

Records

There was an observer on each float who noted the number of times any subject vomited or retched. Within ten minutes after the tests the subjects filled in questionaries which recorded both their sensations at that moment and their recollection of sensations while exposed to motion. All questions and possible answers were randomised. If a subject was so ill that he could not remain on the raft he was removed without interrupting the experiment, and this fact was also recorded.

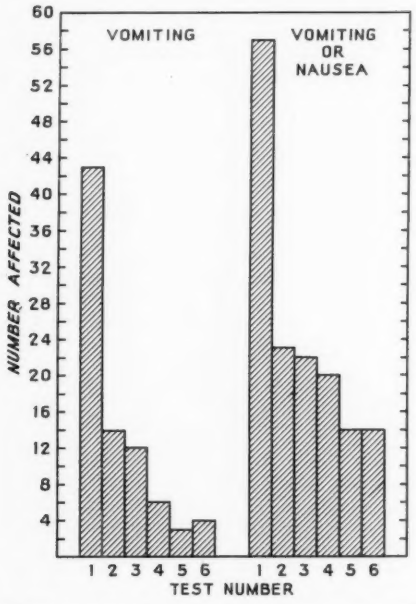

Fig. 1—Effect of habituation to wave motion on vomiting and nausea.

The Tank

The tank was under cover, and it was large enough to allow mooring the floats well apart. The size of the waves was 16–21 in. with a period of 2·7 sec., giving accelerations of 0·3–0·5 *g*. These are approaching optimal conditions for producing motion sickness (Tyler and Bard 1949) and comparable to the motion in previous experiments (Glaser and Hervey 1951, 1952), but the motion was very regular and this was conducive to rapid habituation (see below).

Results

Vomiting and Nausea

Vomiting or retching are evidence of motion sickness, and nausea is a symptom which often deserves treatment in its own rights. It is difficult to differentiate vomiting from retching, and they will be treated as one and the same symptom. All other effects attributed to motion can be confused with side-effects of drugs (Glaser 1953, 1955) and they will be considered separately.

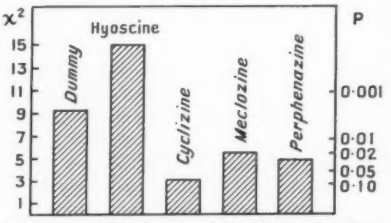

Fig. 2—Statistical value of the effects of various capsules in the first test (results marked * in table II) compared with the effects of no treatment (result marked † in table II).

Fig. 1 shows that the incidence of motion sickness diminished in successive tests, irrespective of treatment. Thus 57 men (74%) were affected by vomiting or nausea in the first test, but only 14 men (20%) in the last. This was the result of habituation both to wave motion (Glaser and Hervey 1952) and to experimental procedures (Glaser and Whittow 1954).

Table II shows the incidence of vomiting and nausea after different treatments. The first test represents a simple controlled experiment without " crossing-over ", and it may be considered on its own. All the 14 men who were given no treatment vomited on that occasion, though they were distributed over six floats. The number of men who were sick was similar after the dummy and after cyclizine, meclozine, or perphenazine, but fewer men were ill after hyoscine than after any other treatment. Fig. 2 shows the significance of the differences between the numbers who vomited after having had no treatment on the first day and those who vomited after having had any of the capsules (the numerical data are given in table II). Significantly fewer men were sick in the first test after having taken the dummy than after having had no treat-

ment at all; and all other substances were also significantly better than no treatment, apart from cyclizine which only appeared to be better than no treatment at the level of 5–10% probability. Taking the first day alone, hyoscine was not significantly better than any of the other treatments, except cyclizine, which differed from hyoscine at the level of $\chi^2 = 3{\cdot}96$, $P \simeq 0{\cdot}05$.

When the results of the whole experiment were considered (table II) hyoscine was clearly the most effective substance, but cyclizine also appeared to have some effect. Of the 9 men who vomited after taking cyclizine only 1 did so after the first test. However, taking either the first three tests, or the experiment as a whole, the total number of subjects affected by vomiting and nausea was similar after taking nothing, the dummy, meclozine, or perphenazine. Though slightly more people were vomiting after having had no capsules than after any of the capsules, neither the dummy, nor meclozine, nor perphenazine were significantly better in this respect than no treatment at all ($\chi^2 < 1{\cdot}7$; $0{\cdot}5 > P > 0{\cdot}1$).

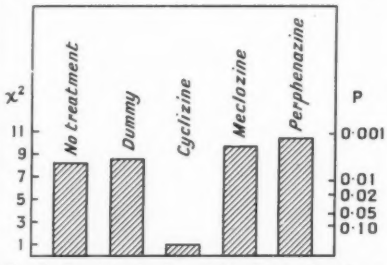

Fig. 3—Statistical value of the effects of various treatments (results marked ‡ in table II) compared with the effects of hyoscine hydrobromide (result marked § in table II): tests 1–3.

Since few subjects were ill in the last three tests (fig. 1), the results as a whole were not affected by them (table II), and for statistical comparisons, therefore, only the first three tests were considered. Fig. 3 compares the total number of subjects with vomiting or nausea after taking hyoscine during the first three tests with the effects of all other treatments, and it shows that hyoscine was significantly better than any of the other treatments except cyclizine. Cyclizine was almost significantly better than meclozine ($\chi^2 = 3{\cdot}28$) and perphenazine ($\chi^2 = 3{\cdot}68$).

Further evidence that cyclizine may have been effective is given in table III, which shows that, by comparison with no treatment or with the dummy capsule, cyclizine gave some protection from motion sickness, although hyoscine gave much better protection. Meclozine and perphenazine appeared to give some slight protection against vomiting when compared with no treatment, but they shared this effect with the dummy.

Other Observations

The subjects' own assessment of the different treatments shows that hyoscine was preferred by the most subjects and considered ineffective by the fewest, while cyclizine was only slightly worse than hyoscine, but meclozine and perphenazine again gave results which were similar to those obtained with the dummy capsule (table IV). The number of subjects who found hyoscine pleasant was significantly greater than the number who found the dummy pleasant ($\chi^2 = 7{\cdot}62$, $0{\cdot}01 > P > 0{\cdot}01$), but the difference between cyclizine and the dummy was not significant ($\chi^2 = 2{\cdot}90$, $0{\cdot}10 > P > 0{\cdot}05$).

Table V gives the incidence of symptoms which may be side-effects of both motion sickness and drug action. Though the questions were randomised, a clear distinction was required between symptoms felt at the moment of completing questionaries and those experienced while exposed to wave motion ten to seventy minutes earlier. The total incidence of symptoms was not high enough to give many significant results, but both on the floats and afterwards the number of subjects who had headaches or felt unwell or suffered from giddiness was the smallest after hyoscine and cyclizine. The incidence of sleepiness was similar after all capsules while the subjects were on the floats; but ten minutes later the incidence of sleepiness was the highest after hyoscine, though the differences were small.

5 subjects, including 1 with tetany, had to be taken off the floats during one or other test because they were prostrate with motion sickness—1 each after receiving no treatment, the dummy, hyoscine, meclozine, and perphenazine.

Recovery of Drugs from Capsules

At the end of the experiment and after the results were known, a random sample of the capsules was placed at the disposal of the firm making meclozine hydrochloride in England. This was done at the suggestion of the makers to enable them to check the code and the filling of the

TABLE III—PERCENTAGE PROTECTION (ALL TESTS)

Treatment	Compared with no treatment		Compared with dummy	
	% protected from vomiting	% protected from vomiting and nausea	% protected from vomiting	% protected from vomiting and nausea
Hyoscine ..	81	82	78	81
Cyclizine ..	58	39	39	43
Meclozine ..	17	0	−5	8
Perphenazine ..	25	−12	7	−5
Dummy ..	31	−7	..	..

Calculated by the formula:

$$\frac{\%\text{ affected after control} - \%\text{ affected after treatment} \times 100}{\%\text{ affected after control}}$$

See Glaser and Hervey (1951, 1952).

TABLE IV—SUBJECTS' ASSESSMENT OF TREATMENTS (ALL TESTS)

Treatment	Pleasant (%)	Unpleasant (%)	No effect (%)
Hyoscine	68	3	29
Cyclizine	61	3	36
Meclozine	44	12	44
Perphenazine	48	11	41
Dummy	48	14	38

TABLE V—SYMPTOMS RECORDED ON QUESTIONARIES (ALL TESTS)

—	While exposed to motion						Ten minutes after motion ceased					
	No treatment	Dummy	Hyoscine	Cyclizine	Meclozine	Perphenazine	No treatment	Dummy	Hyoscine	Cyclizine	Meclozine	Perphenazine
No. of subjects	72	74	73	73	73	73	72	74	73	73	73	73
Symptom:												
Headache	21	19	10	9	14	16	16	18	10	7	13	17
Sleepiness	27	34	36	32	32	37	17	18	25	17	20	23
Feeling unwell	21	26	4	15	24	23	12	9	5	5	8	11
Giddiness	17	25	16	13	17	17	13	10	7	8	14	15

capsules, and they reported that a mean content of only 20·5 mg. of meclozine was recovered. A careful check of the method used in filling the capsules made it seem unlikely that there should have been a systematic loss of this substance during filling, since the only possible errors would have been less than 5% and equally distributed around the intended mean of 25 mg. It seems probable, therefore, that this apparent deficit was due to loss during recovery; but the possibility cannot be completely excluded that the dosage of meclozine hydrochloride, and possibly of all the drugs used in this experiment, was slightly smaller than stated.

Discussion

Hyoscine hydrobromide 1 mg. again gave good protection against motion sickness, and there is no doubt that this drug remains the most effective one for short exposures. The present results thus bear out a prediction made seven years ago that great advances in the treatment of motion sickness were not imminent (Glaser and Hervey 1952). Yet, not all other drugs should be dismissed. Evidence has been produced that meclozine hydrochloride in larger doses was effective on long journeys and when the motion was comparatively mild (Report 1956). Even if the lack of any effect from hyoscine under those conditions was due to the experimental design (see above), the effectiveness of meclozine could not have been due to the way in which those experiments were conducted. The finding that meclozine might be effective on long journeys was confirmed by Arner et al. (1958), though they gave no information from which it could be concluded whether the design of their experiments favoured long-acting drugs. Cyclizine had some effect against motion sickness in the present experiment, and it produced few more side-effects than hyoscine (table v). Cyclizine has also proved effective during long exposures to comparatively mild motion (Report 1956), and it may have a value in this respect.

The fact that the incidence of motion sickness after taking cyclizine was highest on the first day and that from the second day onwards cyclizine appeared to be as effective as hyoscine (table II) may be a freak observation, but it is also possible that cyclizine has its best effect when some habituation to wave motion is already present. This, in turn, could mean that it acts best when the tendency for motion sickness is small, though it could also mean that it specifically enhances habituation.

In the present experiment the dummy capsule apparently protected a significant number of subjects from seasickness in the first test (fig. 2), and it appears to have protected 31% of subjects from vomiting during the entire experiment (table III). Tyler (1946) had previously found that slightly more people were seasick without treatment than after a dummy, though the differences were not significant. Chinn and his colleagues (Report 1956) and Arner et al. (1958) used dummy controls, but it seems possible that apparent effects of drugs against seasickness are sometimes due to psychological reasons. The susceptibilities of subjects can also vary (table I) and the effects of treatment could be related to the susceptibilities of the subjects. This could further explain the divergent findings in different experiments.

Summary

In a cross-over double-blind experiment on the prevention of seasickness during exposures to sharp wave motion lasting an hour, hyoscine hydrobromide 1 mg. gave significantly better protection than other treatments.

Cyclizine hydrochloride (' Marzine ') 50 mg. provided somewhat better protection than an indistinguishable dummy.

Meclozine hydrochloride (' Ancolan ', ' Bonamine ') and perphenazine (' Trilafon ') were no better than a lactose dummy.

In single exposures the lactose dummy appeared to provide significant protection from motion sickness when compared with the effects of no treatment at all.

Our thanks are due to Mr. F. E. E. Smith for much help with the administrative arrangements; to the G.O.C. Southern Command for providing volunteers; to the Superintendent, A.E.W. Haslar, and the Commanding Officer, H.M.S. *Sultan*, for providing facilities; to Prof. J. L. D'Silva, the London Hospital Medical College, for coding the drugs; to Dr. P. Armitage, of the M.R.C. Statistical Research Unit, for providing a randomised code according to the experimental design and for statistical advice; to Mr. C. H. Sykes, chief pharmacist, the London Hospital, for preparing the capsules; to Mr. D. E. Lee, of the M.R.C. Environmental Hygiene Research Unit, for help with statistical work; to Mr. A. J. F. Atkins, Mr. C. G. Barnes, Mr. R. M. Greenwood, Mr. J. A. Rawlings, Mr. C. J. Spivey, and Mr. C. L. W. Webb, of the London Hospital Medical College, for acting as observers; and to the Army volunteers for their cooperation. Drugs were kindly supplied by British Drug Houses Ltd. (' Ancolan ') Schering Corporation (' Trilafon '), and the Wellcome Foundation Ltd. (' Marzine ').

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PERSONALITY DISORDER AND DULLNESS

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THIS paper reports a study into the significance of adverse childhood influences in the development of personality disorder and dullness. Although the patients studied were certified defectives, for reasons given later, it is believed that the findings also apply to those with a Stanford Binet intelligence quotient over 70.

Previous studies of certified and non-certified defectives separately suggested that personality disorder and apparent intellectual dullness could be correlated with adverse influences, the two disabilities being common causes of certification as mentally defective in England (Bourne 1955, Clarke et al. 1958, Craft 1958). To check these findings in one and the same group, yet avoiding the personal bias inherent in diagnosis, patients diagnosed by others as psychopathic were needed, together with controls, so that case-notes could be compared for relevant factors.

It is not easy to find patients in whom all would agree with the diagnosis of personality disorder. Such a group might well be patients requiring transfer from an ordinary mental-deficiency hospital to the State hospitals of Rampton and Moss Side. The superintendent of Rampton has said that most patients there are quite distinguishable from the ordinary run of defectives and show " almost all the textbook manifestations of the psychopathic state " (Mackay 1948). Instead of taking

only those patients whom I thought were psychopathic, personal bias was eliminated by taking fifty consecutive transferred patients over a ten-year period and comparing their case-notes with those of controls. It was postulated that, compared with controls, they would show: (1) a significantly greater number had early adverse influences in childhood; (2) a significantly greater number would show an increase in I.Q. within this period; (3) at follow-up in 1958 fewer patients would have returned to the general community; and (4) as a result of their residual personality deviation these patients would be more likely to commit further offences against the community after discharge.

Method

From 1946 to 1955 inclusive fifty patients were transferred after Board of Control consultation, from the Royal Western Counties Group of mental-deficiency hospitals to Rampton or Moss Side. The case-notes of each of these patients was compared with the case-notes of the next consecutive admission of the same sex who was over school age (15) and of the same legally certified grade of defectiveness. Particular note was taken of: gross poverty in home life; crime in parents or siblings; child neglect, N.S.P.C.C. intervention or court sentence for child neglect; parental deprivation for four years under age 11; lack of a home; illegitimacy; antagonistic parents. These terms are defined, and the method of their assessment is given elsewhere (Clarke et al. 1954, 1958).

Intelligence quotients (I.Q.) were taken from case-notes: in four transferred patients and four controls the I.Q. was below 45; in twenty-two transferred patients and thirty-three controls the I.Q. was between 46 and 69; and in twenty-four transferred patients and thirteen controls the I.Q. was between 70 and 121. These figures are the latest I.Q. and differ from the I.Q. used at initial certification for thirteen transferred patients and three controls, whose I.Q. rose from between 46 and 69 to between 70 and 121 over a five-year period. The tests were made mainly by three graduate psychologists. Where patients had been tested twice in differing years of their adult life the pairs of tests were compared for an increase or decrease in intelligence over this period.

For the third postulate a postal follow-up was carried out to check the whereabouts of patients in the autumn of 1958. The fourth postulate could be tested as a result of information gathered in a previous follow-up (Craft 1959b).

Results

I agree with Mackay (1948) that Cheney's (1934) description of psychopaths applies to most of those transferred to State hospitals who were " characterised largely by emotional immaturity or childishness with marked defects of judgment and without evidence of learning. They are prone to impulsive reactions without consideration for others and to emotional instability with rapid swings from elation to depression . . . standard intelligence tests may be normal, or superior, or . . . not infrequently borderline ". Of the fifty transfers, fourteen were characterised by their violent outbursts to others, including murder, whilst sixteen had paroxysms of extreme self-violence leading to suicidal lacerations with glass or to dashing themselves against the walls or floors. Another twelve had personality disorder associated with epilepsy, encephalitis, kernicterus, or syphilis; there was one rapist, two violent homosexuals, and five who repeatedly committed arson or thefts with violence. I considered forty-five (90%) had personality disorder.

ADVERSE INFLUENCES IN CHILDHOOD

Influence	State hospital patients	Controls	Significance
Deprivation of one or both parents for four years before the age of 11	34 (68%)	10 (20%)	$P<0.001$
Childhood neglect and N.S.P.C.C. intervention	22 (44%)	8 (16%)	$0.001<P<0.01$
Court sentence in childhood	4 (8%)	0	N.S.
No home at all	19 (38%)	1 (2%)	$P<0.001$
Illegitimacy	14 (28%)	5 (10%)	$0.02<P<0.05$
Gross poverty in home	12 (24%)	7 (14%)	N.S.
Record of crime in parents or siblings	9 (18%)	7 (24%)	N.S.
Irregular schooling	19 (38%)	23 (46%)	N.S.
Hostile parents	5 (10%)	11 (22%)	N.S.
Patients with 2 of above factors	35 (70%)	18 (36%)	$0.01<P<0.001$
Patients with 3 of above factors	28 (56%)	8 (16%)	$P<0.001$

N.S. = not significant.

Postulate 1.—The table shows the results of the case-note study. More State hospital patients are affected by two or more adverse childhood influences than in the control series ($0.01<P<0.001$). Of the fifteen State hospital patients not so affected, five had a history of brain damage and two were imbeciles with intelligence quotients below 46.

Postulate 2.—Most State patients had been absent on transfer for long periods, but twelve State-hospital patients and twenty-two controls had been tested in different years over the age of fifteen, with either the pair of Stanford Binet forms M and L, or the Wechsler forms 1 and 2. Ten State hospital patients showed an increase in I.Q. (ranging from 5 to 33 points), one showed no change, and one a decrease of 8 points. Of twenty-two controls thirteen gained from 1 to 6 points, seven were unchanged, and six lost from 1 to 5 I.Q. points. In an average of 4·9 years State-hospital patients made an average gain of 11·8 I.Q. points, whilst over an average of 5·0 years the controls gained an average of 1·4 points. Including mixed pairs of I.Q. tests, twenty State-hospital patients improved and three deteriorated in intelligence or were unchanged, whilst thirteen controls gained and sixteen lost or remained unchanged in I.Q. over the years. This is a significant number for those showing increments compared with decrements, where $0.01<P<0.001$.

Postulate 3.—At follow-up in 1958, an average of 13·1 years after admission, nine State-hospital patients had returned to the community, and were either in residential licensed employment or had been completely discharged, compared with twenty-seven controls ($P<0.001$). Hence the postulate is supported.

Postulate 4.—Using a different follow-up (Craft 1959b) of three hundred and fifteen ex-defective patients who had been discharged from the Acts for a period averaging 5·3 years, it was found that among ten patients previously in State hospitals, two were unemployed and eight employed, whilst five gave a history of periods of unemployment requiring National Assistance, and five had been in continuous employment since discharge. State hospital patients here showed the same proportions in employment record as the remaining three hundred and five patients. None of the State patients had committed further indictable community offences compared with 9% of the remaining three hundred and five. Postulate 4 does not appear to be supported, although the number of cases is too small to be any more than suggestive.

Discussion

Before considering the influence of detrimental early environment on personality disorder and intelligence, the discrepancy between the two series in age of admission should be noted; forty State patients were admitted in their teens, but only twenty-eight controls were in this age-group. The difference, which is not statistically significant ($0.20<P<0.10$), is probably due to the greater number of State patients lacking parents or a home,

and who therefore came under care at an earlier date.

The results show that among defectives there is a positive correlation between early adverse childhood experiences and later behaviour disorder serious enough to require transfer to a State institution. Most of these patients have been held to merit the diagnosis of psychopath and with this I would agree. Thirty-five out of fifty of the present patients had two or more adverse factors in childhood and it is noteworthy that five of the remainder had damage to the brain and two were imbeciles. Parental deprivation, both paternal and maternal, was found to show the closest correlation with later behaviour disorders and, although this is the most that can be said, the findings are supported by Bowlby (1951) and Henderson (1942). Furthermore, previous studies (Craft 1958) have shown that 26–33% of different groups of ascertained and certified defectives had non-violent personality disorder; and some of these are certainly included in the 20% of controls who suffered parental deprivation.

Although most of the patients were in their late teens the increases in tested intelligence occurred in patients of all ages. None were psychotic. The increases occurred in the same type of deprived patient and were of a similar order to those found previously (Clarke et al. 1958, Craft 1958). The validity of such changes is discussed by the Clarkes and their conclusion, modified to suit the present patients, seems appropriate: that, after initially adverse childhood influences, any reasonably stimulating environment in adult life may allow deprived patients to reach their full complement of endowed intelligence. Postulates 3 and 4 were designed principally to test whether this conclusion also applied to personality deviations. Using Schneider's (1954) concept of personality disorder as a deviation from the statistical (or community) norm, community pressures and the process of maturation would be expected to reduce this deviation over the years.

Gibbens et al. (1955) and Henderson (1942) suggest that those with personality disorders tend to mature. As assessed by postal follow-up in 1958, the proportion of State hospital patients returning to the general community was disappointingly low, although earlier discharges had been reasonably successful; but more optimistic results have been recorded (Craft 1959b). Compared with their particular controls, former deviants were found to be equally successful in employment and marriage, but were more liable to commit further offences against the community. There is some evidence, therefore, for an improvement in social adaptation over the years among those with personality disorders. Methods which can increase the speed of such maturation are at present on trial at Balderton.

Summary

Compared with a control group a significantly greater number of adult defectives with personality disorder had been exposed to early adverse influences in childhood, and showed an increase in tested intelligence during adult life. I.Q. increased by as much as 33 points in the absence of psychosis. The findings are similar to those of other studies with deviants, many of whom could, and later did, show social adaptation. The findings throw doubt on excessive dependence on intelligence tests for the diagnosis of mental defect. The results of these tests must be considered in the light of social history and clinical findings.

I should like to thank Dr. David Prentice for his help and encouragement and Mr. Harry Fairchild for his independent assessment of case-notes. The superintendents of Rampton, Moss Side, Hortham, Stoke Park, Sandhill Park, Leavesden, and Harperbury kindly cooperated in the follow-up. The study was part of a research programme, financed by the Group Management Committee (summarised in Craft 1959a).

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TRIMEPRAZINE TARTRATE FOR PREMEDICATION OF CHILDREN

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"THE adult may safely be treated as a child, the converse can lead to disaster." So writes William E. Ladd (1958).

The introduction of modern anæsthetic drugs which allow a smooth and pleasant induction of anæsthesia, without the application of a face-mask, has decreased the amount of sedation needed before operation. Most anæsthetists now agree that all that is necessary for preparing adults for operation is an explanation of the procedure and mild sedation.

For children, however, many different methods of premedication are recommended (Anderson 1952, Burstein 1953, Eckenhoff 1953, Harrison and Maytom 1957, Leigh and Belton 1948, Rendell 1954, Tajima 1956, Wright and Tetirick 1953). Indeed no single drug is ever likely to be satisfactory for all children, because the degree of sedation required varies with the age of the child.

For sedation before operation, children may be divided into three age-groups: $1^1/_2$–$3^1/_2$ years, $3^1/_2$–7 years, and 7 years and upwards. The child aged $1^1/_2$–$3^1/_2$ should be asleep on arrival at the operating-theatre, and this is best achieved with rectal thiopentone. In children over 7 the drugs used for premedication in the adult can be given (Anderson 1952).

In children between $3^1/_2$ and 7 years the choice of premedication is more difficult as these children are the most upset by entering hospital, and the usual drugs are less satisfactory. The object in this group is to produce a state intermediate between the deep narcosis sometimes produced by rectal thiopentone sodium and the minor degree of hypnosis produced by papaveretum and scopolamine in safe dosage. Rectal thiopentone sodium is seldom used at this age, partly because one wishes to avoid the passage of tubes per rectum in these children, and partly because this drug produces an unnecessary degree of narcosis—especially in those over the age of 5. The drugs most commonly used in this hospital in children aged from $3^1/_2$ to 7 years are pentobarbitone or quinalbarbitone sodium (by mouth) or papaveretum and

scopolamine in comparatively heavy dosage. Barbiturates by mouth have a very unpleasant taste no matter how the powder may be disguised. It is difficult to administer capsules to small children and indeed it may be unwise because the capsules may dissolve slowly and exert their effect when not required, or they may be vomited and aspirated on induction. Our practice is to administer the barbiturate as a powder disguised in a spoonful of orange juice; even so a number of children are overcome by the unpleasant taste and promptly vomit the drug. Furthermore, because of irregular absorption, barbiturates by mouth may exert a variable action, and they may cause an increase in gastric secretion. Postoperative restlessness due to lack of analgesia is another disadvantage. Papaveretum and scopolamine administered according to weight may produce inadequate hypnosis in children aged from $3^1/_2$ to 5 years unless the dose is increased to the point where it causes excessive respiratory depression. For this reason it is seldom used on children under 3 stone. Accordingly the dose of a particular drug in children depends on body-weight, but the type of drug used for premedication depends to a certain extent on age.

Thus there is considerable room for improvement in premedication in children between the ages of $3^1/_2$ and 7. In this paper we report the trial of a new phenothiazine derivative, trimeprazine tartrate (' Vallergan '), in these children.

Clinical Trial

Trimeprazine is a newly developed phenothiazine derivative which can be regarded pharmacologically as intermediate between promethazine and chlorpromazine. It has possibly an even greater anti-histamine action than promethazine and its central actions—including an anti-emetic one—are comparable to those of chlorpromazine, although it has little of the latter's anti-adrenaline action. In addition it has a powerful spasmolytic action on smooth muscle. Its duration of action is less than that of chlorpromazine.

Up to the present the drug has been given mainly by mouth, although occasionally it has been used by intramuscular or intravenous injection.

We compared this new drug with quinalbarbitone sodium, for its efficacy in producing sleep; thus a placebo could not be used as well as our intention was to do more than abolish anxiety. The smaller children, who were the most important patients in the trial, would not swallow capsules and unfortunately we were unable to disguise the extremely unpleasant taste of the barbiturate powder. Trimeprazine tartrate on the other hand is available as a palatable syrup, and capsules for the barbiturates did not provide an answer to the problem—for this reason the idea of a double-blind trial had to be abandoned. Because of this the drugs were given in the form in which they would be used in everyday practice—trimeprazine tartrate as a syrup containing 4 mg. per ml. and quinalbarbitone sodium as a powder in a spoonful of concentrated orange juice.

The series consisted of two hundred cases; one hundred and sixty of these patients had tonsillectomy performed and forty patients had an operation to correct strabismus.

Alternate cases had quinalbarbitone or trimeprazine as premedication. The drugs were given by mouth $1^1/_2$ hours before operation, and followed by atropine intramuscularly some 30–40 minutes before operation. Barbiturate dosage was 30 mg. per stone, and the dosage of trimeprazine was 2 mg. per lb. On arrival in the anæsthetic room the patient was assessed by one of us and usually the assessor did not know which drug had been given to a particular patient.

The anæsthetics used were 50% cyclopropane and 50% oxygen for about one minute followed by nitrous oxide, oxygen, and ether. Patients undergoing tonsillectomy were not intubated and anæsthesia was maintained with the Boyle-Davis gag or a tonsil hook (Waugh's method). In the latter method adenoidectomy is performed after tonsillectomy and deep anæsthesia is necessary at the end of the procedure, in contrast to the technique using the Boyle-Davis gag. This accounts for the long recovery-time to some extent.

The rate of postoperative recovery was also determined. In tonsillectomy a tongue clip is inserted at the end of operation to maintain the airway and the time of removal of this clip provided a useful comparison of the duration of effect of the two drugs. Restlessness, as evidenced by the need for sedation, and vomiting following operation, were also noted in the two groups.

Results

Trimeprazine syrup was easily administered to most of the children (there is always a minority who reject any " medicine ", however palatable), and none of the one hundred patients to whom it was administered vomited the drug afterwards. Quinalbarbitone was disliked by all the children, resulting in some cases in retching, and in two cases out of one hundred the barbiturate was vomited shortly after administration.

In each series there was little difference in the degree of consciousness or cooperation, as assessed in the anæsthetic room before operation.

In each series just over 50% were lightly asleep—i.e., they did not stir in quiet surroundings and tolerated 50% cyclopropane and 50% oxygen from a mask provided the mask did not touch the face. A further 25–30% were cooperative whether awake or drowsy, and 13% were uncooperative whether awake or drowsy. In each series two patients vomited during induction.

The postoperative state of the patients showed a greater difference between the two series than the preoperative state (see accompanying table).

POSTOPERATIVE STATE

Method of assessment	Quinal-barbitone sodium series	Trimeprazine series
Interval from end of operation to removal of tongue clip	24 min.	21 min.
Incidence of postoperative vomiting ..	39%	26%
Incidence of cases requiring postoperative sedation	12%	4%

Discussion

As previously stated, for children of $3^1/_2$ to 7 years the object of premedication is to produce sleep. Ideally, the drug should be given by intramuscular or subcutaneous injection before operation; but failing this it must be given by mouth. The drug must therefore be palatable and the effective dose must be contained in a small quantity of fluid. An effect of short duration is obviously an advantage in order to allow a reasonably rapid recovery from anæsthesia. A decrease in restlessness and vomiting after operation is an obvious additional advantage.

To what extent does trimeprazine tartrate fulfil these requirements? The barbiturates are recognised as being supreme in the production of sleep and trimeprazine is about equivalent to quinalbarbitone for this purpose. In

each series just over 50% of the children were lightly asleep, and about a further 30% in each series were drowsy and cooperative, or awake and cooperative—i.e., in a satisfactory state. Only 13% were definitely unsatisfactory, uncooperative, or restless.

It is worth emphasising, however, that transport to theatre in a lift, or careless handling of the children, will reduce the number arriving in the theatre in a satisfactory state.

The syrup used in this series contained 4 mg. per ml. and was very palatable, although a large volume of solution had to be given. More recently we have used a 6 mg. per ml. syrup (' Vallergan ' Forte) and the quantity of this for inducing sleep is reasonable—e.g., 13·5 ml. to a 40 lb. child $1^1/_2$ hours preoperatively.

In the period following operation the table shows that the interval between the end of operation and removal of the tongue clip was about the same in the quinalbarbitone as in the trimeprazine series: thus there is no objection to the latter because of delay in postoperative recovery.

The incidence of postoperative vomiting was 39% in the quinalbarbitone series but only 26% in the trimeprazine series, although this is not statistically significant ($P > 0.05$). The high incidence of vomiting in each series is due to the ether anæsthesia and to the swallowing of some blood from the tonsillar fossa.

The incidence of cases requiring postoperative sedation was 12% in the control series and 4% in the trimeprazine series, but this could also be due to chance ($P > 0.05$). Sedation was never given except in cases of exceptional restlessness and this accounts for the low figure in each group. The impression of the nursing staff was that children were much quieter postoperatively after premedication with trimeprazine than after quinalbarbitone. This, if so, would be an important advantage of trimeprazine over quinalbarbitone, as restlessness following operation is one of the objections to barbiturates for premedication.

Summary and Conclusions

In a group of two hundred young children, a new phenothiazine derivative, trimeprazine tartrate (' Vallergan '), has been compared with quinalbarbitone sodium as a premedicant, and its effect on recovery and vomiting after operation has also been assessed.

Its advantages are that it is palatable and easy to administer. Its hypnotic effect proved to be equal to that of quinalbarbitone. It did not prolong the period of recovery to a " safe state ", and fewer children vomited or were restless after operation, though the difference was not statistically significant.

Its disadvantage is that with the present preparation the quantity of syrup which has to be taken is somewhat large, but it is hoped to concentrate the solution even further.

We are grateful to the nurses of the Hospital for Sick Children for their cooperation throughout this investigation. We wish to thank May & Baker Ltd. for supplies of ' Vallergan ' and for their advice.

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CORD-BLOOD FINDINGS IN ABO HÆMOLYTIC DISEASE

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HÆMOLYTIC disease in the newborn is caused as frequently by ABO incompatibility as by rhesus (Rh) antibodies (Halbrecht 1951, Hsia and Gellis 1954). Fortunately, however, ABO hæmolytic disease is usually mild, and few cases require treatment by exchange transfusion. In nearly all severe cases the mother's serum contains anti-A or anti-B hæmolysins (Crawford et al. 1953), but, because these antibodies are present in about 20% of all pregnant women, an antenatal test for hæmolysins is of no value for the routine prediction of ABO hæmolytic disease.

Our own practice is to examine the mother's serum for hæmolysins when there is a history of a previous baby being severely jaundiced or stillborn, and the father's blood is of an incompatible ABO group. Should hæmolysins be present, oxalated and clotted samples of the baby's cord blood are collected and tested to determine the extent of the disease and whether exchange transfusion is necessary. Cord-blood samples are tested similarly when an exceptionally potent anti-A or anti-B hæmolysin (i.e., a titre greater than 1/8) is a chance antenatal finding during a first pregnancy or when the other children have been normal.

Initially we based our decision regarding the need for an exchange transfusion on the same criteria as for Rh hæmolytic disease—namely, a cord hæmoglobin below 100% (14·8 g. per 100 ml.), or a serum-bilirubin greater than 3 mg. per 100 ml. But it soon became evident that these criteria may not be generally applicable in cases of ABO incompatibility, and we decided therefore to study a series of infants in order to correlate the cord-blood findings with a careful clinical assessment, and to find, if possible, a more accurate way of predicting severity in ABO hæmolytic disease.

Procedure

ABO hæmolytic disease is most frequent in babies born of group-O mothers (Rosenfield 1955).

Oxalated and clotted samples of cord blood were collected from babies at Southmead Hospital whenever the mother was known to be group-O and there were no Rh antibodies in the serum. The samples were examined for ABO-group, hæmoglobin, and serum-bilirubin. When the baby's group was A or B, the red cells were examined for sensitisation by the direct anti-globulin test, and for increased fragility, using the methods recommended by Rosenfield (1955), and a reticulocyte-count was made.

ABO hæmolytic disease usually shows clinically as moderate or severe jaundice starting during the first twenty-four hours after birth. Each baby was therefore examined daily for obvious

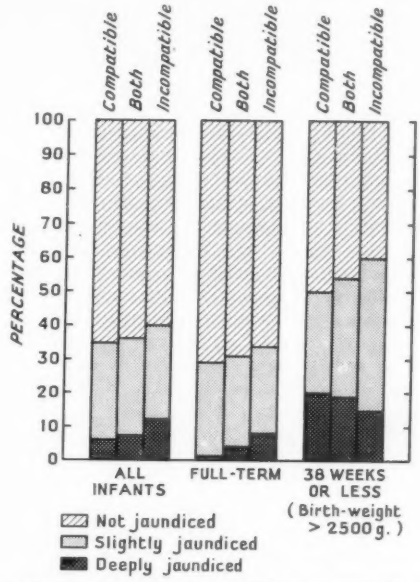

Fig. 1—Incidence of jaundice in 575 infants of group-O mothers.

jaundice during the first five days of life by one observer (T. V.), the assessment being made without knowledge of the cord-blood findings. Intravenous samples were taken at intervals from babies developing jaundice, and were examined for serum-bilirubin content. A serological examination of the baby's and mother's blood was made to determine that the jaundice was not due to immune blood-group incompatibility of another type.

Results

Samples of cord blood were collected from 575 babies. In 393 the baby's blood-group was O—i.e., "compatible"; in 182 it was A or B—i.e., "incompatible".

Neonatal Jaundice

The incidence of clinical jaundice in the 575 babies is summarised in fig. 1 and table I. The incidence of slight jaundice is not significantly different in compatible (29%) and incompatible (28%) babies. By contrast, deep jaundice was more frequent in ABO incompatible babies. This difference is brought out more clearly when full-term babies only are studied. Of 450 full-term babies, 8% of ABO incompatible babies showed deep jaundice compared with 1% of compatible babies.

TABLE I—INCIDENCE OF NEONATAL JAUNDICE IN 575 INFANTS OF GROUP-O MOTHERS

	Cases	Not jaundiced		Slightly jaundiced (serum-bilirubin < 10 mg. per 100 ml.)		Deeply jaundiced (serum-bilirubin > 10 mg. per 100 ml.)	
		No. of cases	%	No. of cases	%	No. of cases	%
All babies:							
Total	575	367	64	167	29	41	7
Compatible ..	393	257	65	113	29	23	6
Incompatible ..	182	110	60	54	28	18	12
Full-term babies:							
Total	450	311	69	122	27	17	4
Compatible ..	306	216	71	85	28	5	1
Incompatible ..	144	95	66	37	26	12	8
Babies aged 38 weeks or less (birth weight < 2500 g.):							
Total	92	43	46	32	35	17	19
Compatible ..	61	31	50	18	30	12	20
Incompatible ..	31	12	40	14	45	5	16
Premature babies:							
Total	33	13	..	13	..	7	..
Compatible ..	26	10	..	10	..	6	..
Incompatible ..	7	3	..	3	..	1	..

A group of 92 babies, immature by age of gestation but weighing over 2500 g., showed a much higher overall incidence of deep jaundice (19%) and the influence of ABO incompatibility had disappeared. 20% of the compatible babies and 16% of the incompatible babies in this group were deeply jaundiced. During our study 2 babies developed severe jaundice and required exchange transfusion for hyperbilirubinæmia. Both were group-O (compatible) and both were immature babies.

Cord-blood Findings

Hæmoglobin (fig. 2).—526 cord-blood samples were suitable for hæmoglobin check (by M.R.C. grey wedge photometry). In 347 group-O babies the hæmoglobin ranged from 79% (11·7 g. per 100 ml.) to 153% (22·3 g.), with a mean of 117·7% (17·2 g.). Neither in range nor in mean was this significantly different from the cord-blood hæmoglobin of the 179 incompatible babies (range 74–148%; mean 118%).

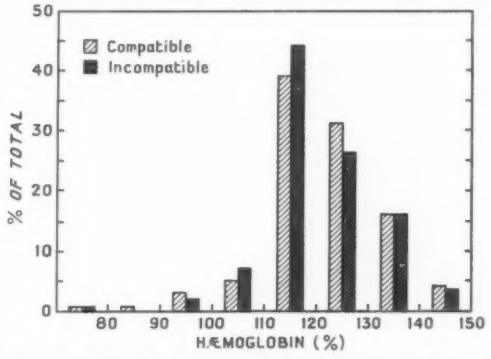

Fig. 2—Distribution of cord hæmoglobin in 526 infants of group-O mothers.

7 ABO incompatible babies had a cord-blood hæmoglobin below 100% (14·8 g. per 100 ml.), but so had 13 babies who were group-O and compatible. 1 baby with a cord-blood hæmoglobin of 98% (14·3 g.) showed clinical and serological evidence of ABO hæmolytic disease, but none required treatment.

Serum-bilirubin (fig. 3).—Total serum-bilirubin was estimated by Malloy and Evelyn's method (1937) in 212 cord-blood samples (107 compatible and 105 incompatible).

The technique was modified for 0·2 ml. of serum. Standards were prepared from bilirubin supplied by Roche Products Ltd., and all tests were performed by one senior technician using a Hilger spectrophotometer throughout. To assess reproducibility, 10 replicate determinations were carried out on each of 10 samples with bilirubin levels ranging from 1·15 to 27·07 mg. per 100 ml. The standard error ranged from 0·034 to 0·264.

Whilst the mean did not differ significantly between the two groups of cord-blood samples (compatible 1·80 mg. per 100 ml.; incompatible 1·84), there was a difference in range (compatible 0·6–3·5 mg. per 100 ml.; incompatible 0·5–4·7). In 7 ABO incompatible babies and 3 compatible babies the cord serum-bilirubin was greater than 3 mg. per 100 ml. 3 of the incompatible babies showed clinical

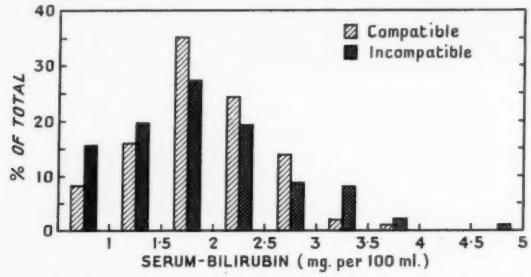

Fig. 3—Distribution of cord serum-bilirubin in 212 infants of group-O mothers.

and serological evidence of ABO hæmolytic disease, but none needed treatment.

Saline fragility.—Rosenfield (1955) found that the cord blood in 31 of 337 ABO incompatible babies showed an increased osmotic fragility by his screening test in 0·52% saline.

We examined 113 cord-blood samples from incompatible babies during our present study by Rosenfield's technique. The increase in osmotic fragility was moderate in 17 of these and gross in 4. But there was no correlation between these findings and the clinical progress, since only 4 of the 17 babies with a moderately increased fragility, and 1 of the 4 with a grossly increased fragility, later became jaundiced.

Reticulocytes.—Reticulocyte-counts made on cord-blood samples from 103 incompatible babies showed a range of 0·6–7·2%, with a mean of 2·5%. At birth 6 babies had reticulocyte-counts in the range of 6–7·2%, but none of these developed jaundice or other clinical evidence to suggest ABO hæmolytic disease.

Direct anti-globulin test.—Rosenfield's modification of the direct anti-globulin test (1955) was performed on samples of cord blood from 106 compatible babies and all (182) incompatible babies. A positive result (weak) was obtained in 1 case only (case 2, table II). This baby was group-B, and had hæmolytic disease, but this was not severe enough to need treatment. In 5 other babies who developed hæmolytic disease (table II), the direct anti-globulin test was negative.

Discussion

6 of the 575 babies from whom cord blood was collected showed clinical and laboratory evidence of ABO hæmolytic disease. The essential findings in these babies are summarised in table II. Each became deeply jaundiced and, except in case 4, jaundice was noticeable within twenty-four hours of birth. None of the babies showed pallor nor enlargement of the liver or spleen either at birth or later. Apart from jaundice, their neonatal course was unremarkable. Among the 575 infants studied, these were the only ones who became jaundiced within thirty-six hours of birth. Thus it appears that clinically the only consistently reliable sign of ABO hæmolytic disease is early jaundice (within twenty-four hours) in an infant without Rh or other blood incompatibility. This early jaundice serves to differentiate cases of ABO hæmolytic disease from those of severe "physiological" jaundice due to inadequate conjugation of bilirubin. Early jaundice does not necessarily mean that treatment will be required, but it does indicate the need for close observation and frequent estimations of serum-bilirubin.

The cord-blood examination of these 6 cases showed no single consistent feature which might be claimed as diagnostic of ABO hæmolytic disease. By contrast with Rh hæmolytic disease, in which the direct anti-globulin test is almost always positive, this test was negative in 5 and doubtfully positive only in 1. This may, of course, be because there are not yet available anti-human-globulin reagents specific for the antibody globulins (or antigen-antibody complex) associated with ABO hæmolytic disease. Although in 3 cases the hæmoglobin was well below the general mean of 118%, in only 1 was it lower than 100% (98). The serum-bilirubin ranged from 1·2 to 4·7 mg. per 100 ml., but in 4 of the 5 blood samples tested it was raised above the general mean of 1·84 mg. It is noteworthy that whilst the lowest cord-bilirubin level (1·2 mg. per 100 ml.) was found in a full-term baby who later developed the deepest jaundice (maximum bilirubin at seventy-two hours 23 mg.), the baby whose cord hæmoglobin was 98% and serum-bilirubin 4·7 mg. had a maximum bilirubin of 9 mg. only, and the mildest clinical disease. Saline-fragility tests and reticulocyte-counts in 4 of the babies later showing hæmolytic disease proved of no value in diagnosis or prognosis.

The only laboratory finding common to each of the 6 cases was the presence of an anti-A or anti-B hæmolysin in the mother's serum. This adds further support to the opinion that ABO hæmolytic disease is unlikely except when these antibodies are present (Mollison 1956), and examination of the mother's serum for hæmolysins is important in confirming the clinical diagnosis. But the strength of the incompatible hæmolysin gave no guide to

TABLE II—ESSENTIAL FINDINGS IN 6 BABIES WITH ABO HÆMOLYTIC DISEASE

Case no.	1	2	3	4	5	6
Cord blood:						
ABO group ..	A	B	B	A	A	A
Hæmoglobin (%) ..	106	113	122	104	116	98
Serum-bilirubin (mg. per 100 ml.)	..	3·1	1·2	3·3	2·9	4·7
Direct anti-globulin	Neg.	±	Neg.	Neg.	Neg.	Neg.
Red-cell fragility ..	..	Mod'te	Slight	Slight	Slight	..
Reticulocytes (%)..	..	1·8	3·4	1·8	1·4	..
Mother's serum:						
Hæmolysins ..	−	+ +	−	−	±	+ + +
Immune agglutinins	Neg.	+ (anti-B)	Neg.	Neg.	Neg.	Neg.
Clinical details:						
Onset of jaundice (after birth)	16 hr.	24 hr.	24 hr.	36 hr.	24 hr.	12 hr.
Maximum serum-bilirubin (mg. per 100 ml.) (Time after birth)	14·9 (48 hr.)	17·5 (48 hr.)	23·0 (72 hr.)	14·9 (72 hr.)	14·0 (96 hr.)	9·0 (24 hr.)

TABLE III—FINDINGS IN 13 CASES OF ABO INCOMPATIBILITY, WITH RAISED CORD SERUM-BILIRUBIN OR LOW CORD HÆMOGLOBIN, NOT REQUIRING TREATMENT

Case no.	ABO group	Serum-bilirubin (mg. per 100 ml.)	Hb (%)	Reticulocytes (%)	Length of gestation (weeks)	Clinical comments
Cases with clinical and serological evidence of ABO hæmolytic disease:						
1	B	3·1	133	1·8	40	Jaundiced within 24 hr.
2	A	3·3	104	1·8	40	Jaundiced within 36 hr.
3	A	4·7	98	..	40	Jaundiced within 12 hr.
Cases with no evidence of ABO hæmolytic disease:						
4	A	3·3	..	2·6	40	No jaundice
5	A	3·9	109	..	40	Slight jaundice at 48 hr.
6	A	3·9	131	2·4	40	No jaundice
7	B	3·2	123	2·6	40	No jaundice
8	A	1·5	99	1·3	40	Slight jaundice at 72 hr.
9	A	1·1	98	2·9	40	No jaundice
10	A	..	98	2·6	39	No jaundice
11	A	0·8	94	3·1	35	Slight jaundice at 48 hr.
12	A	0·5	90	..	40	No jaundice
13	A	..	74	3·2	40	No jaundice, not anæmic

the clinical course in these 6 cases, the strongest hæmolysin being found in the least affected baby (case 6, table II).

Of the 105 incompatible babies, 13 had a cord-blood hæmoglobin below 100% (14·8 g. per 100 ml.) or a serum-bilirubin greater than 3 mg. per 100 ml. Had the mother of any such baby given a history of a jaundiced or stillborn child, we might have thought an exchange transfusion was indicated. In fact none of these babies became sufficiently anæmic or jaundiced to require transfusion, and it is clear that these two tests, which have proved such a valuable guide in the management of Rh hæmolytic disease, are not of the same help in ABO hæmolytic disease. The findings in these 13 babies are summarised in table III.

In addition to the 6 cases of ABO hæmolytic disease in this study (none needed exchange transfusion) we have observed several other cases of ABO hæmolytic disease of which 7 required exchange transfusion. 4 of these infants were born in Southmead Hospital, and 3 were admitted from elsewhere because of early jaundice. All 7 were transfused because of hyperbilirubinæmia, and this is the greatest hazard facing the infant with ABO hæmolytic disease. Kernicterus is preventable by means of exchange transfusion. But it is difficult to define precisely the indications for this operation. The level of indirect bilirubin in the blood is the best guide, and cases cannot be properly managed without frequent serum-bilirubin estimations. In our experience with jaundiced infants of all types, a level of 25 mg. per 100 ml. is the upper limit of safety. However, it is important to realise the limitations of such an arbitrary figure. Serum-bilirubin determinations are consistent within one laboratory but vary between different laboratories, and susceptibility to kernicterus is affected by factors such as immaturity, anoxia, and the baby's age at the time of maximum hyperbilirubinæmia. The decision to transfuse may be modified by the facilities and skill available. As the cord blood gives no predictive information as to the need for exchange transfusion, it is probably reasonable to suggest that a rapidly rising serum-bilirubin in the first three days of life is an indication for transfusion, whereas if the serum-bilirubin level only reaches the danger zone at five or six days, the baby may be watched. Because of the rarity of kernicterus in full-term babies with ABO hæmolytic disease, it may be justifiable to be rather more conservative in management than with Rh hæmolytic disease or hyperbilirubinæmia of prematurity.

This study has confirmed the finding of Fortunato and Rondinini (1950) that severe neonatal jaundice occurs more often in ABO heterospecific pregnancies than in homospecific pregnancies. It suggests also the possible importance of even minor degrees of immaturity as a factor in jaundice in the newborn.

Summary and Conclusions

Clinical assessment and cord-blood examination of 575 babies born of group-O mothers has shown the need for caution in the interpretation of cord-blood findings in infants thought likely to show ABO hæmolytic disease.

Cord-hæmoglobin and serum-bilirubin levels did not correlate well with the clinical progress of the baby, and a cord hæmoglobin below 100% or a bilirubin above 3 mg. per 100 ml. is not necessarily an indication for an exchange transfusion in this condition. The modified direct anti-globulin and saline-fragility tests proposed by Rosenfield (1955), and reticulocyte-counts, did not facilitate diagnosis.

Deep jaundice appeared earlier and more frequently after ABO heterospecific pregnancy than homospecific pregnancy. The highest overall incidence of neonatal jaundice was in babies immature by age of gestation, and it was not influenced by ABO incompatibility.

Exchange transfusion for ABO hæmolytic disease is not necessary unless the serum-bilirubin rises to dangerous levels. This can be determined only by close observation and repeated measurement of the serum-bilirubin.

We wish to thank Mr. C. N. Chapman, A.I.M.L.T., for undertaking the serum-bilirubin estimations, the senior technical staff of the Regional Transfusion Centre for assistance with the hæmatological investigations, and the midwifery staff at Southmead Hospital for the collection of cord-blood samples.

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FULMINATING ECLAMPSIA TREATED BY HYPOTHERMIA

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IN eclampsia sedation with barbiturates, chlorpromazine, pethidine, and promethazine has been extensively employed (Hughes and Savage 1957). Shears (1957) collected reports of 127 prenatal cases treated in this way.

In reviewing the use of hypothermia in various conditions, Adams-Ray (1956) does not report eclampsia; but Ezes et al. (1957) used " moderate hypothermia "—no temperature chart was given—in a case of eclampsia, starting treatment on the 13th day of coma. They recommended tracheotomy, although they did not use it in their case.

We have been unable to find any reference to the use of controlled hypothermia in the treatment of fulminating eclampsia. The following is a report of the successful use of this method.

Case-report

Mrs. A., aged 23, who was in the 35th week of pregnancy, was admitted to Royal Air Force Hospital, Ely, on Oct. 17, 1958, in coma and having fits.

She had complained of feeling unwell earlier in the morning. Her husband had gone to fetch a doctor, and on his return he had found her lying unconscious at the foot of the stairs. She had been seen as an antenatal patient 2 days before admission, at which time, although there was slight œdema of the ankles, her blood-pressure was within normal limits and her urine free of albumin.

She was supposed to have suffered from fits as a child.

Examination

The fits observed on admission were bilateral in onset, and clonic, with persisting spasm between attacks; there was no spontaneous micturition. She had a slight bruise of the left orbital region, consistent with a fall; and radiography revealed a fracture of the nasal bones, without displacement, so accounting for some bleeding from the nostrils. There was no fracture of the skull.

There was bilateral orbital œdema, but retinoscopy revealed no abnormality.

Her ankles were swollen and albumin was found in the urine; the blood-pressure, however, was not significantly raised.

Course

A provisional diagnosis of acute eclampsia was made and caesarean section was performed on the same day. The baby, a well-formed male weighing 5 lb., was transferred immediately to the premature neonatal unit at Addenbrooke's Hospital, Cambridge, where several slight fits were observed, but these ceased, and he made good progress.

Contrary to expectations the mother did not recover consciousness after operation; and she continued to have one fit every hour or so. Respiration was embarrassed and the airway could be maintained only by a cuffed endotracheal tube. Her condition deteriorated, in spite of sedation with pethidine, chlorpromazine, and promethazine administered by intravenous drip, and by next day, when she had had 16 fits, it seemed likely that she would die as a result of the vicious circle: cerebral anoxia—fits—further anoxia. Intravenous thiopentone injections alleviated the fits, but the response was not sufficiently swift to be effective.

At this hospital we had found that, in cases of coma arising from head injury, convulsions were controlled readily by hypothermia. We accordingly decided to treat our patient as a case of head injury in coma, for which the three requisites are tracheotomy, hypothermia, and intravenous therapy with careful control of electrolyte and fluid balance.

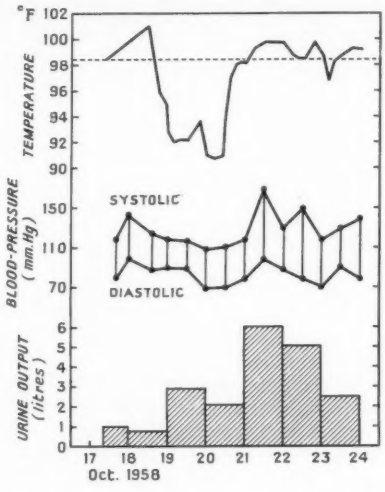
Tracheotomy and Hypothermia

Tracheotomy was performed at midday on Oct. 18, 1958. The anæsthetics used were nitrous oxide, oxygen, and halothane, and these controlled the convulsions. An infusion containing pethidine 200 mg., chlorpromazine 100 mg., and promethazine 100 mg. in 500 ml. physiological saline solution was administered intravenously through a polyethylene tube introduced into the left great saphenous vein. A second bottle, connected to the same system by a T tube, was used for fluid and electrolyte replacement. Heparin and cortisone were added to prevent clotting and venous thrombosis respectively; routine biochemical investigations were undertaken every day. The patient was then cooled by exposure to cold air from an electric fan.

As we expected the coma to last several days we intended to lower the rectal temperature to about 88 F. But the fits ceased from the time anæsthesia was induced for tracheotomy and the patient recovered consciousness (to such an extent that she was able to recognise her husband by name) some 20 hours after commencement of cooling—that is, on the morning of Oct. 19. At this time her temperature was 92 F. Further cooling was stopped and the process discontinued on Oct. 20. Her temperature rose, as shown in the figure. Variations of blood-pressure paralleled the temperature, but at no time was there pronounced hypertension.

Subsequent Progress

Moderate diuresis had commenced on Oct. 19 when cooling was well established. Chlorothiazide was given when the temperature had risen to normal and produced a profound diuresis, as shown in the same figure. On admission, the urine had contained 0·3 g. protein per litre, but by Oct. 27, 10 days later, it had fallen to 0·1 g. per litre, with a urinary output of 2·4 litres. At this time also the urinary specific gravity had risen to 1012, having fallen to 1004 at the height of diuresis (on Oct. 21), when the urinary volume was 6·3 litres.



(Crown copyright.)

Composite graph to show rectal temperature, urinary output, and recordings of systolic and diastolic blood-pressure during the critical period of treatment.

Œdema subsided, and the tracheotomy tube was removed on Oct. 23: subsequently the tracheotomy wound closed spontaneously. Thereafter her recovery was uneventful. On first regaining consciousness she complained of some blurring of vision, but this did not persist and there was no evidence of cerebral damage as a result of anoxia.

The baby was restored to his mother and both left hospital in good health on Nov. 8, 22 days after the onset of the attack.

Summary and Conclusions

The successful use of controlled hypothermia and tracheotomy in a case of fulminating eclampsia is described.

We wish to thank the Director General of Medical Services, R.A.F., for permission to publish.

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FATAL ENDOCARDITIS ASSOCIATED WITH Q FEVER

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OUR patient was a man aged 60, a maintenance engineer, and he was admitted to the Cardiff Royal Infirmary on March 5, 1958. He had the classical appearance of subacute infective endocarditis with obvious café-au-lait coloration, gross finger clubbing of both hands, and splinter hæmorrhages under the fingernails.

3 weeks previously he had had an influenza-like illness from which he had not fully recovered, remaining weak, easily tired, and feverish. For 5 days he had had pain, swelling, and tenderness in the left calf. There was slight œdema of the calf and ankle, and a tender deep vein was palpable. There was a harsh (grade 3) aortic systolic murmur. The blood-pressure was 120/90 mm. Hg, and the pulse-rate was regular at 100 per min. There was no splenomegaly. He was very ill and a little confused, with a temperature of 102° F.

In the absence of a previous rheumatic illness, the nature of the aortic lesion was uncertain. Treatment with penicillin was started at once, while investigations were made.

Virus Studies

Complement-fixation (C.F.) tests for influenza A, B, and C, psittacosis-lymphogranuloma, adenovirus, lymphocytic choriomeningitis, and mumps were negative throughout the course of the illness. Tests for cold and *Streptococcus MG* agglutinins and heterophile antibodies were negative also.

Q fever C.F. showed a titre of 1/32 on March 7, rising to 1/64 on March 21, and remaining unchanged on April 3. The titre had fallen to 1/8 at the time of death.

Other Investigations

Some 40 blood-cultures were made during the month after admission; 33 were sterile, while coagulase-negative staphylococci were grown seven times.

There was occasional slight proteinuria, with a few leucocytes and small numbers of hyaline and granular casts in the urine.

The Wassermann and Kahn reactions were negative. The electrolytes were normal. The blood-urea level remained under 46 mg. per 100 ml. For the first 2 months a leucocytosis of about 12,000 cells per c.mm. (with 75% neutrophils) and an erythrocyte-sedimentation rate (E.S.R.) of 50 mm. in the 1st hour persisted. The white cell-count then dropped to about 8000 and the E.S.R. to 25 mm., and persisted until death.

Treatment and Progress

Penicillin (8 mega-units daily) and anticoagulants were given for the first 4 days. The dose was then increased to 16 mega-units, and streptomycin 1 g. daily and oral iron were added. After 2 weeks the penicillin and streptomycin were replaced by erythromycin 2 g. daily. This was continued for the duration of the illness.

The patient's general condition improved slowly until May. No more splinter hæmorrhages appeared, but congestive cardiac failure supervened, and mersalyl and digitalis were given. In mid-July it seemed that the endocarditis had been successfully treated. After a brief period of paranoid psychosis, however, he died suddenly on July 29.

Postmortem Findings

The pericardial sac contained about 250 ml. of straw-coloured fluid, and there were a few pericardial petechial hæmorrhages. The wall of the left ventricle was thickened. There was a large irregular friable vegetation on the anterior cusp of the aortic valve, associated with considerable destruction and perforation of the cusp. The posterior cusps were partially fused, thickened, and calcified. There was also partial fusion, but no thickening, of two cusps of the pulmonary valve. The endocardium of the posterior wall of the left ventricle showed an area of pallor 3 cm. in diameter. Numerous greyish-white spots, 0·5–1 cm. in diameter, were distributed throughout the muscle of the left ventricle.

There were large bilateral pleural effusions. The lungs were collapsed and firm, with a few small peripheral infarcts. The spleen was small and was surrounded by dense adhesions, especially on its diaphragmatic surface. Pale blotchy areas about 0·5 cm. in diameter were visible in the cortex of the kidneys.

Histology

The aortic cusps showed considerable collagen formation with a fibrinoid change in the superficial layers. The overlying thrombus was organising. Many large mononuclear cells and foci of inflammatory cells (mainly neutrophils) were present. The left ventricle also showed subendocardial collagen formation. The white foci seen naked eye were areas where the muscle fibres had become necrotic and swollen. Groups of muscle fibres were disrupted and œdematous. There was an irregular fibrosis. A small branch of the left coronary artery was completely occluded by thrombus.

The kidneys showed acute tubular necrosis. No lesions of focal endocarditic glomerulonephritis were found. There was an acute bronchitis with very little pulmonary consolidation.

Careful search of gram-stained sections of all the tissues, and especially the heart-valve thrombus, failed to detect any bacteria. Machiavello's stain, however, showed obvious intracytoplasmic structures. These varied from coccobacillary forms, about 0·5 μ in diameter, to large irregular ovoids about 3 μ in diameter. A few red coccobacillary forms were seen amongst the necrotic fibres near the endocardial surface of the left ventricle. The stain was used also on the heart-valve thrombi from a case of *Streptococcus viridans* and a case of staphylococcal endocarditis. Nothing resembling the red-staining objects described above was found.

Comment.—The primary heart lesion was undoubtedly a relatively early stage of calcific aortic stenosis. The superimposed endocarditis was unlike the usual type of bacterial endocarditis in that, although the process was histologically active, no bacteria could be found. The particles shown by Machiavello's stain resemble both the rickettsial coccobacillary forms and the morulæ described in the experimental animal. The myocardial lesions resembled those seen in acute rickettsial fevers such as typhus and there were no microembolic foci of the type found in bacterial endocarditis.

Isolation of Rickettsiæ

Suspensions of aortic valve and spleen diluted to 1/5, 1/10, 1/50, and 1/250 were inoculated intraperitoneally into adult guineapigs. Two animals were used for each dilution.

Both guineapigs inoculated with the 1/5 dilution of spleen, and one of the two inoculated with aortic valve died after 12 days. Impression smears of the spleens of these animals, when stained by Machiavello's method, showed large numbers of intracellular bodies resembling rickettsiæ.

4 weeks after inoculation, serum from the surviving guineapigs was tested for *Rickettsia burneti* C.F. antibodies. These were present to a titre of more than 1/2000 in the animals inoculated with spleen suspension, but were not detectable in those with aortic-valve suspension.

The spleen of the animal which died after inoculation of aortic-valve suspension showed rickettsia-like bodies; it was emulsified and inoculated intraperitoneally into guineapigs in dilutions varying from 10^{-1} to 10^{-6}, using two animals for each dilution. The animals which were given the 10^{-1}, 10^{-2}, and 10^{-3} dilutions died within 10 days of inoculation and the rickettsia-like bodies were again seen in spleen smears. The serum of surviving animals taken after 6 weeks gave C.F. titres for Q fever of 1/1000 or more. None of the animals had C.F. antibodies before inoculation.

We present the details of this case in the hope that pathologists may be interested enough to re-examine material from cases of infective endocarditis in which blood-cultures were persistently negative, and histological examination failed to demonstrate bacteria in the vegetations.

Summary

A fatal case of infective endocarditis superimposed on calcific aortic stenosis is described.

Rickettsia-like bodies were demonstrated in the heart-valve thrombus by Machiavello's stain.

Rickettsia burneti was isolated from the aortic valve and spleen by guineapig inoculation.

We wish to thank Dr. William Phillips, consultant physician, United Cardiff Hospitals, for permission to publish this case.

Preliminary Communication

TREATMENT OF DIABETES INSIPIDUS WITH HYDROCHLOROTHIAZIDE

WHEN the urinary output of salt is raised by taking more in the diet, the volume of urine increases in diabetes insipidus by about the same proportion as in normal subjects. A single dose of chlorothiazide increases the urinary excretion of salt, and normally this leads to diuresis. In diabetes insipidus, however, chlorothiazide has an *antidiuretic* action.[1] The volume of the urine does not change significantly after the first dose of chlorothiazide, so the extra salt discharged results in an increase in concentration of the urine. Moreover, when treatment is continued the saluresis soon abates, but the urine remains concentrated so long as the drug is given, and its volume is reduced by about half.

Recently a more potent saluretic agent, hydrochlorothiazide, has become available. This might offer practical advantages in the treatment of polyuria; but in addition it would be of theoretical interest to find out whether its antidiuretic potency is correspondingly enhanced, as one would expect if the saluretic and antidiuretic actions were interdependent.

COMPARISON WITH CHLOROTHIAZIDE

It had previously been found that 320 mg. of chlorothiazide per kg. of body-weight, when incorporated daily into the food of a rat with experimentally induced diabetes insipidus, reduced its water intake by about half. Preliminary tests showed that 8 mg. of hydrochlorothiazide per kg. had a roughly equivalent effect. A formal assay was carried out with doses of 40, 80, 160, and 320 mg. of chlorothiazide per kg. and 1, 2, 4, and 8 mg. of hydrochlorothiazide per kg. Doses were given in random order, each for 4–5 days, to four severely polyuric rats. Fig. 1 shows the relations between the percentage depression of daily water intake and the logarithm of the dose. Analysis of variance showed no difference between the slope of the lines, and indicated a relative potency of 50 : 1 (5% confidence limits 32 : 1 and 76 : 1; $\lambda = 0{\cdot}13$). The precision of the assay reflects a high order of reproducibility of the effect, and explains why so few animals were needed. Further tests showed that little additional reduction of fluid intake followed doses even eight times as high as the highest employed in the assay, and the maximum effect of each drug was the same. In all respects, then, except in the dosage required, the antidiuretic action of these two drugs was identical.

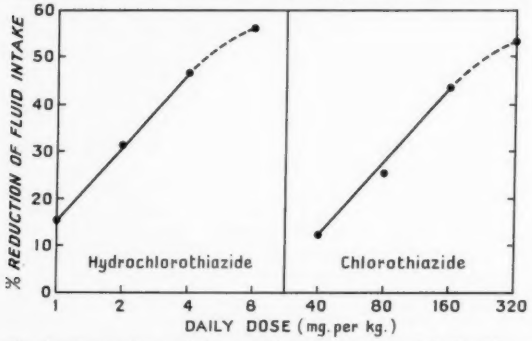

Fig. 1—Comparison of the antidiuretic potency of hydrochlorothiazide with that of chlorothiazide.

1. Crawford, J. D., Kennedy, G. C. *Nature, Lond.* 1959, **183**, 891.

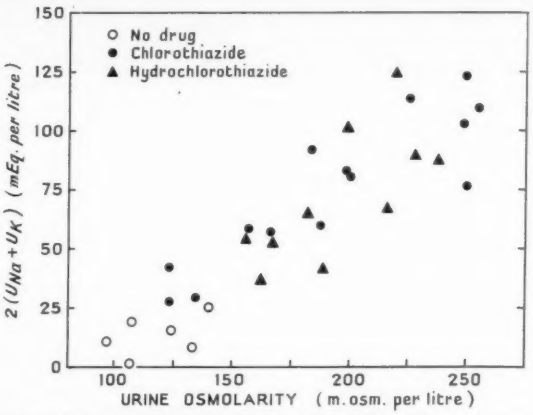

Fig. 2—The relation between the initial saluretic effect of hydrochlorothiazide and chlorothiazide and urine osmolality.
Since urine volume was almost constant the concentration values of the ordinate scale are virtually interchangeable with values for output of Na and K.

The acute saluretic potency of the two drugs was tested in fasted normal rats. Appropriate doses were given by gavage in dilute alkaline solution made to a total volume of 10 ml. with tepid water. Urine was then collected for 6 hours and the volume, osmolality, and Na and K concentrations were measured. Possibly because of differences in the rate of absorption the urinary solute excretion was too variable to yield a reliable comparison of potency of the drugs. However, most of the test rats excreted considerably more solute than did control animals, with a negligible change in urine volume. In consequence, as is shown in fig. 2, the slope of the best-fitting straight line relating twice the sum of the concentrations of urinary Na+K to the total osmolality of the urine—0·82—indicates that the increase in these cations together with their complementary anions in urine almost completely accounts for the change in osmolality. The simplest explanation of this finding, we feel, is that the drugs interfere with the reabsorption of cation, without water, in that part of the distal tubule where, in the absence of antidiuretic hormone, the final dilution of urine is thought to occur.

THE ANTIDIURETIC EFFECT

It is more difficult to explain why the volume of urine decreases when treatment is continued. Since the urine *remains* concentrated, we assume that the interference with distal tubular function lasts as long as the drug is given. The return of the net sodium output to normal levels must therefore indicate a compensating increase in absorption by some other part of the nephron. If this took place in the proximal segment it would be accompanied by passive reabsorption of water, so diminishing the urine volume. A compensation of this kind might be mediated through increased adrenal activity. To investigate this possibility both normal rats and rats with diabetes insipidus have been adrenalectomised and exposed to hydrochlorothiazide. Those which were simply adrenalectomised were still able to curtail the excess sodium excretion after the initial drug exposure and survived under prolonged treatment with chlorothiazide or hydrochlorothiazide. In those with diabetes insipidus also, the saluresis after hydrochlorothiazide proved to be transient and the antidiuretic action was unimpaired. Thus,

adaptation to the initial saluretic action of these drugs appears to be independent of the adrenal.

THE EFFECT IN MAN

In preliminary tests on four volunteer medical students who on several occasions maintained a state of overhydration and maximal urine flow for from 4 to 6 hours, 250 mg. of chlorothiazide caused greater saluresis and concentration of the urine than 12·5 mg. of hydrochlorothiazide. The ratio of potency of the two drugs in man appeared therefore to be less than 20 : 1. Accordingly 100 mg. of hydrochlorothiazide was adopted as the dose likely to be equivalent to 1 g. of chlorothiazide in clinical diabetes insipidus.

Thus far, the response to hydrochlorothiazide has been fully studied in but one case of diabetes insipidus—a man of 26 with the vasopressin insufficiency type, made available by the kindness of Prof. M. L. Rosenheim. The results will be published in detail later, but the response to 100 mg. of hydrochlorothiazide was virtually identical with that to 1 g. of chlorothiazide in a similar case previously observed.[1] In each case the dose was that conventionally used to secure a full saluretic action. Although these initial results suggest that hydrochlorothiazide may have a part in the treatment of diabetes insipidus in man, more prolonged tests are being undertaken to assess its long-term value.

We are grateful to Prof. R. A. McCance for his interest and support, and to Miss Sheila Pledger, Miss Pat Pledger, and Mr. Brian Misson for their assistance.

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Reviews of Books

Modern Trends in Diseases of the Vertebral Column

Editors: REGINALD NASSIM, B.M., F.R.C.P., physician, St. George's Hospital and Royal National Orthopædic Hospital, London; H. JACKSON BURROWS, M.D., F.R.C.S., F.R.A.C.S., orthopædic surgeon, St. Bartholomew's Hospital and Royal National Orthopædic Hospital, London. London: Butterworth. 1959. Pp. 303. 75*s*.

INTEREST in disorders of structure and function in the spine is not confined to orthopædic surgeons, and many patients with symptoms referred to their backs belong to the domain of the general physician, the endocrinologist, or the psychiatrist. This book deals with its subject in this broad sense, and orthopædic surgeons number only 5 of its 15 contributors.

Six chapters deal with general aspects of the investigation and treatment of backache: the anatomy of the spine, congenital anomalies, radiological examinations, and the role of spinal biopsy. The remainder are concerned with special conditions such as osteoporosis, degenerative disease, and tuberculosis. All of them are ably written by experts, and those on scoliosis (Prof. J. I. P. James) and ankylosing spondylitis (Dr. F. Dudley Hart) are particularly noteworthy for clear advice on common problems.

In many instances of backache, however, no organic disease can be demonstrated. These patients are often the despair of all who treat them, and it is no surprise that Dr. W. Tegner, in his authoritative and convincing article, has to acknowledge that there are no advances to report in the management of this type of pain in the back.

The Johns Hopkins Hospital and the Johns Hopkins University School of Medicine

A Chronicle. VOL. 2. 1893-1905. ALAN M. CHESNEY, M.D., dean emeritus of the medical faculty, Johns Hopkins University. Baltimore: Johns Hopkins Press. London: Oxford University Press. 1958. Pp. 499. 48*s*.

THIS second volume runs from Oct. 1, 1893, when the School of Medicine opened with 15 men and 3 women students, until June 30, 1905, the end of the academic year which saw the resignation of Dr. William Osler as professor of medicine and physician-in-chief, and his departure for Oxford. It is a record of significant happenings in two closely related institutions in the order in which they befell, each academic year being dealt with in a separate chapter.

Among the lavish illustrations (plans and photographs of buildings and wards, student groups, and formal and informal portraits of members of the staff) is a frontispiece of Osler as the presiding genius hovering over the hospital building. There can be little doubt that while Osler was at Johns Hopkins he was the most inspiring of all the clinical teachers with whom the students came in contact.

The text includes curricula, letters, and anecdotes, and abounds with famous names—Halsted, Kelly, MacCallum, Howell, Cushing, Thayer, McCrae, and many others. This is a worthy account of a great medical school and hospital at what was possibly its period of greatest progress. But it gives no inkling of the extent or significance of the contributions to scientific knowledge made by members of the staffs of the two institutions during this time.

Cell and Tissue Culture

JOHN PAUL, M.B., PH.D., M.R.C.P.E., director, H.E.R.T. tissue-culture laboratory, and honorary lecturer, department of biochemistry, University of Glasgow. Edinburgh: E. & S. Livingstone. 1959. Pp. 261. 30*s*.

LABORATORY workers and clinicians who are unfamiliar with cell culture will find a very lucid description of both classical and new methods in this book, which is based on the Tissue Culture Association's summer course, of which Dr. Paul is director. It is full of sound practical advice, presented simply and concisely, and there is also a useful introductory section on elementary cytology.

Most existing textbooks on cell culture do not deal with the dispersion of tissues into cell suspensions and the growth of liberated cells on glass substrata. These techniques, which are of great interest and much value in virology, are very adequately described by Dr. Paul. In the section describing the collection of fowl plasma cannulation of the femoral artery is not mentioned, yet many feel that this is superior to carotid-artery cannulation. A description of the culture of mammalian ova would have been valuable, for they tend to be overlooked as a source of cytological material.

We warmly recommend this excellent monograph to those seeking guidance about current tissue-culture techniques. The publishers are to be congratulated on its high quality and low price.

The Care of the Geriatric Patient

Editor: E. V. COWDRY, PH.D., SC.D., director of Werse Cancer Research Laboratory, Washington University School of Medicine. St. Louis: C. V. Mosby. London: Henry Kimpton. 1958. Pp. 438. 60*s*.

AMONG the nineteen chapters by 22 authors, the only British contribution is by Dr. J. H. Sheldon, who writes the most interesting article in the book, on Geriatrics Round the World. There are introductory sections on the relation of the doctor to his elderly patients and on the psychology of ageing. Clinical aspects covered include medicine, surgery, anæsthesia, and dentistry of old age; there is a useful chapter on nursing problems; and the therapeutics and rehabilitation of the elderly are discussed. It is clear that the problems of the American geriatrician do not differ from those in this country, but the chapters on the social aspects of geriatrics have little relevance for British readers. Inconsistencies are hard to eradicate in symposia of this kind (here, for example, the use of

chlorpromazine is advocated in one chapter and decried in another). There are still very few good books on the management of geriatric patients and this one undoubtedly helps to fill a gap.

Medulloblastoma

BENJAMIN L. CRUE, JR., L.C.D.R., M.C., U.S.N., neurosurgical service, U.S. Naval Hospital, San Diego, California. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 206. 43*s*.

IT is often helpful to see large problems discussed in terms of a particular example, and this book about a certain histological group of tumours throws into relief a great many questions concerning the genesis, nature, and treatment of malignancy. These matters are here given a thorough airing in a well-informed and informative monograph. The author takes the view that medulloblastoma is incurable, but he gives fair consideration to the instances of long survival either in older individuals or in those treated by radiation. He pleads for accurate diagnosis by biopsy before treatment is initiated, and condemns blind irradiation as a means of excluding medulloblastoma. Cairns is quoted: "There are already too many people going about the world quite blind, but otherwise well, from whom benign cerebellar tumours have been removed too late to save vision." And again Bailey et al.: "To sacrifice even one of these children" (with cerebellar astrocytoma) "whose outlook with the aid of competent neurosurgery is so good, to the mere desire of ruling out an inoperable and hopeless tumour is inexcusable." In this and other ways, the book shows wisdom.

The Management of Fractures and Dislocations

ANTHONY F. DEPALMA, M.D., professor of orthopædic surgery, Jefferson Medical College. Philadephia and London: W. B. Saunders. 1959. 2 vols. Pp. 973. £12 5*s*.

THIS comprehensive atlas devoted to injuries of bones and joints is designed to give the essential points in the management of individual injuries, and its approach is cataloguical rather than discursive. Its basis is a series of line drawings (no radiographs are used)—which is an economical and on the whole effective technique for the display of simple fractures and dislocations. The illustrations are accompanied by concise notes about the main clinical features, and include all stages in the management of the injury and its complications. The style is necessarily didactic.

The earlier pages deal with the general principles of fracture treatment, and include a short section on pathological fractures. The illustrations in this section are of little value, and the list of common causes of pathological fractures includes some of the rarest of bone conditions. The management of individual injuries is described with much practical detail, and the indications for closed and open methods of treatment are fully considered; but the problems of internal fixation do not seem to get adequate attention. Inevitably some of the appliances described are not readily available in this country, but most of the systems of treatment which Professor DePalma advocates are simple and sound, and where he is unorthodox he also indicates more generally accepted methods.

The book will appeal particularly to those who are new to the treatment of bone and joint injuries or who deal with them rarely. In the treatment of some of the more severe injuries, particularly those of the chest and the pelvis, they may find it inadequate, but for the management of most of the common injuries of the skeleton it is comprehensive and concise.

British Obstetric and Gynæcological Practice (2nd ed. *Gynæcology*. London: Heinemann Medical Books. 1958. Pp. 891. 105*s*.).—Although this is a large book it is eminently readable and some of the chapters are admirable expositions. Edited by Sir Eardley Holland and Mr. Aleck Bourne, it is steadily finding its place in British medical literature. In general, only minor alterations have been necessary since the first edition appeared $3^1/_2$ years ago, but one or two chapters have been extensively revised. An attempt has been made to correct anomalies inevitable in a first edition, but some contributors still write mainly for undergraduates while others clearly intend their chapters for specialists in training. The first edition did not refer to granuloma inguinale; the condition is now described in two different chapters with contradictory advice about treatment. One or two ill-defined but important subjects, such as iliac-fossa pain, are still only briefly mentioned. The quality of paper is greatly improved and the layout and uniformity of headings are now excellent.

Medical Directory 1959 (London: J. & A. Churchill. In two parts. 84*s*.).—The 115th issue of these familiar red volumes contains 91,206 names. It also offers a great deal of useful well-arranged information on such topics as hospitals, universities, Ministries, and medical societies and periodicals.

New Inventions

A NEW INTRAMEDULLARY NAIL COMBINED INTRODUCER AND EXTRACTOR

INTRAMEDULLARY nailing of shaft fractures of long bones, such as the femur, occasionally presents technical difficulties. One such difficulty is impaction of the nail as it is driven into cortex or if the selected nail is too thick. In such circumstances it is useful to have the nail introducer and extractor combined in a single unit. Nails sharpened at both ends progress along the medullary canal more easily than the blunt-ended nails; and this is particularly useful when the retrograde method is used. Using nails which have been sharpened and slotted at each end, the new instrument illustrated here can be rapidly engaged with or disengaged from the selected nail.

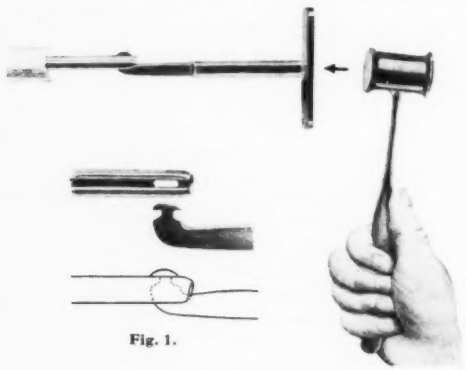

Fig. 1.

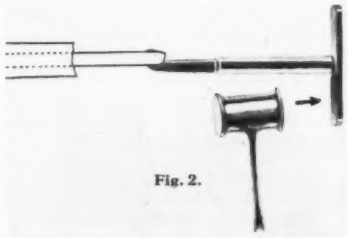

Fig. 2.

Fig. 1 shows the instrument in use, and the inset shows the details of the shape of the end of the instrument and the fitting of this to the nail. Fig. 2 shows the loosening of an impacted nail by a blow on the reverse side of the T-shaped handle. This instrument has been used successfully in the orthopædic theatres in Aberdeen Royal Infirmary for over two years. It is supplied in stainless steel by Messrs. John Bell & Croyden, London.

T. L. CARR
CH.M. Aberd., F.R.C.S.

Aberdeen Royal Infirmary

THE LANCET

LONDON 25 APRIL 1959

Epidemiology of Toxoplasmosis

FOR the host it is important to live on good terms with his parasites; but for the parasite it is equally important to live on good terms with its host, and in this the protozoon, toxoplasma, is notably successful. Serological evidence indicates that it has infected from 4% (Navajo Indians)[1] to 94% (Guatemalans)[2] of adult human populations. The Eskimos of Alaska, alone of those tested, are apparently free.[1] In this country between 20% and 40% appear to have been infected.[3]

In addition to its wide geographical distribution toxoplasma has an amazingly wide host range. It seems to be capable of infecting all species of mammals, many birds, and some reptiles, though not amphibians.[4] Nor is it just an occasional invader. Between 5% and 60% of cats and dogs,[5–10] 34% of wild rabbits,[11] 5–50% of cattle,[1] 40% of goats,[1–5] 15–40% of pigs,[5 12–14] and 5–60% of sheep,[1 13] have been found infected. In this issue (p. 881) Mr. RAWAL describes serological evidence of toxoplasma infection in 12% of pigs and 11% of one and 21% of another series of sheep slaughtered in Sheffield. Still more definite evidence of infection is given by his isolation of the parasite from 6% of his second series. A higher incidence in samples taken on some days than others suggests a varying prevalence, which FELDMAN and MILLER [1] found in herds of cattle.

Despite the vast amount of infection, toxoplasma rarely does harm. The fœtus is particularly susceptible, and congenital infection is well known. This may be manifested by jaundice, enlargement of liver and spleen, and skin rashes; such cases have simulated hæmolytic disease of the newborn.[15] Alternatively it may give rise to hydrocephaly (which may not be externally apparent), chorioretinitis, cerebral calcification, and convulsions or other manifestations of nervous involvement.[16] The most constant of these signs is chorioretinitis, which is found in 80% of cases.[17] This may be the only sign and escape recognition till later in life, perhaps when the child first tries to read. Some 20–35% of cases of chorioretinitis are thought to be due to toxoplasma infection [18–20]; how much of this is congenital and how much acquired is not known. Because antibodies are rarely found in young children, except in the first few months of life when they may result from passive maternal transfer, and because they steadily increase in frequency with advancing years, it may be assumed that infection can be acquired throughout life. Usually infection after infancy passes unrecognised. Sometimes, however, it causes lymphadenopathy; some 5–7% of cases of "glandular fever" unaccompanied by a Paul-Bunnell reaction are due to toxoplasmosis.[21 22] Rarer manifestations are myocarditis [23 24] (which has been found in this country), encephalitis,[25] and a severe and often fatal typhus-like illness.[26]

The infection, being so prevalent and so widespread, might be expected to be transmitted in some simple way. Yet, in man at least, we still know of no natural means of transmission other than congenital, and this accounts for very few cases. For congenital infection to occur it is commonly held that the mother must become infected during pregnancy. WEINMAN,[27] however, believes that it can result from chronic infection, and toxoplasma is known to persist for up to 32 months in the human body.[28] In mice (for what this is worth) BEVERLEY found that infection in successive pregnancies, even up to the fifth litter after the initial infection, was not uncommon; and he observed congenital transmission of toxoplasma from mother to daughter through five generations.[29] So in mice infection could continue without introduction from outside. This is, however, most unlikely to apply to man; for if it did, antibodies would not be rare in infants or increase with age.

The multiplicity of possible sources of infection complicates the search. In the vicinity of one congenitally infected baby, toxoplasma was found in cats, mice, pigeons, hens, and ducks.[30] Man's domestic animals have often been suspected, and there is little doubt that persons in close contact with dogs or cats ill with toxoplasmosis can acquire infection from them, through fæces, urine, or saliva. This does not account for cases where there has been no close contact with a pet, and it is hard to reconcile with the finding of BEVERLEY and his colleagues that toxoplasma antibodies were as common in people who did not keep dogs as in those who did.[11] The existence of a parasitæmia, the superficial resemblance of toxoplasma to leishmania and trypanosoma, and the reports in a few cases of tick-bites preceding illness has led to investigations, so far fruitless, of transmission by a blood-sucking arthropod.[31] Rodents become infected when they eat the flesh of animals dead of toxoplasmosis. This suggested that human infection

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2. Wright, W. H. *Amer. J. clin. Path.* 1957, **28**, 1.
3. Beattie, C. P. *Trans. R. Soc. trop. Med. Hyg.* 1957, **51**, 96.
4. Jacobs, L. *Ann. N.Y. Acad. Sci.* 1956, **64**, 154.
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10. Lainson, R. *Ann. trop. Med. Parasit.* 1956, **50**, 172.
11. Beverley, J. K. A., Beattie, C. P., Roseman, C. *J. Hyg. Camb.* 1954, **52**, 37.
12. Weinman, D., Chandler, A. *J. Amer. med. Ass.* 1956, **161**, 229.
13. de Roever-Bonnet H. *Docum. Med. geogr. trop.* 1957, **9**, 336.
14. Jacobs, L. *Publ. Hlth Rep., Wash.* 1957, **72**, 872.
15. Bain, A. D., Bowie, J. H., Flint, W. F., Beverley, J. K. A., Beattie, C. P. *J. Obstet. Gynæc. Brit. Emp.* 1956, **63**, 826.
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19. Jacobs, L., Naquin, H., Hoover, R., Wood, A. C. *Bull. Johns Hopk. Hosp.* 1956, **99**, 1.
20. Perkins, E. S., Beverley, J. K. A. *Trans. ophthal. Soc. U.K.* 1957, **77**, 159.
21. Siim, J. C. *Ann. N.Y. Acad. Sci.* 1956, **64**, 185.
22. Beverley, J. K. A., Beattie, C. P. *Lancet*, 1958, ii, 379.
23. Bengston, E. *Cardiologia*, 1950, **17**, 289.
24. Potts, R. E., Williams, A. A. *Lancet*, 1956, i, 483.
25. Sabin, A. B. *J. Amer. med. Ass.* 1941, **116**, 801.
26. Pinkerton, H., Henderson, R. G. *ibid.* p. 807.
27. Weinman, D. *Ann. Rev. Microbiol.* 1952, **6**, 281.
28. Couvreur, J. Thesis, Paris, 1955, p. 215.
29. Beverley, J. K. A. Personal communication.
30. Gibson, C. L., Eyles, D. E. *Amer. J. trop. Med. Hyg.* 1957, **6**, 990.
31. Jacobs, L. *ibid.* 1953, **2**, 365.

might come from infected meat. It was with this in mind that RAWAL examined pigs and sheep for toxoplasmosis with the successful results reported in this issue. As he points out, human infection could come from eating raw mutton—and, he might have added, raw pork. It is, however, hardly conceivable that enough raw meat is eaten in this country to account for the high prevalence of human infection; and, if raw meat were responsible, infection would be expected, by analogy with trichinellosis, to be commoner in women than in men.[32] In fact the prevalence is the same in each sex. Evidence that cooked meat does not cause toxoplasma infection was obtained by RAWAL when he examined sera from vegetarians and meat-eaters in Bombay: the prevalence of infection was the same in each group.[33]

The way, or more probably ways, in which toxoplasmosis is spread have yet to be found. A lead worth following was given by CATHIE [34] when he found toxoplasma in the saliva of a child. There are few fomites so widely spread, and in the search for an animal source it should not be forgotten that the animal with which man is most in contact is man.

Renal Function in Burned Patients

AT present, when a great deal of new work is being done on the kidney, a short pause for reflection on what we know but do not fully understand about renal structure is timely. The nephron itself is a familiar structure, and the function of the glomerulus and tubule is well understood in general terms. But is it always remembered that there are two quite different types of nephron in the human kidney? There are the familiar ones situated in the cortex, with a short loop of Henle; but there are also the juxtamedullary nephrons, fewer but rather larger, and with long loops of Henle penetrating to the inner zone of the medulla. Nor do the differences end here. The renal artery ends in a series of radial vessels—the interlobar arteries—which pass between the renal pyramids to the junction of the cortex and medulla. Here they turn to form a series of arches—the arcuate vessels—whose soffits are roughly parallel to the edge of the cortex. From these arcuate vessels arise the interlobular arteries, which pass outwards through the cortex, each supplying some glomeruli. The juxtamedullary glomeruli, on the other hand, receive their blood-supply either directly from the arcuate vessels or else from an interlobular vessel very shortly after its origin. Moreover the efferent vessels from the superficial (cortical) glomeruli are smaller than those from the juxtamedullary glomeruli. It is hard to avoid the impression that there are two sets of glomeruli, and that the blood-flow through them depends on different factors. This impression is strengthened by the preservation of the juxtamedullary cortical zone in acute cortical necrosis of the kidney.[35–37]

The changes in renal function that follow trauma of various kinds have long been recognised. Histological observation of the kidney in such circumstances [38–40] focused attention largely on the tubules, and in 1950 BULL et al.[41] described a characteristic pattern of renal failure associated with "acute tubular necrosis"—a condition held to result from over sixty causes.[42] The initial phase, lasting hours or days, is marked by oliguria or anuria, which was at first believed to arise from mechanical blocking of the tubules, or from interference with the blood-flow through the kidney owing to a general rise in intrarenal pressure. Subsequently DE WARDENER [43] found that this pressure was not raised in dogs with tubular necrosis induced by ligation of the renal artery, and MUNCK [44] found no rise in tension in five patients with oliguric failure in whom the tip of a catheter was wedged in a renal vein. BULL et al.[41] went on to say that the glomerular-filtration rate (G.F.R.) was reduced to about the same extent as the renal blood-flow (R.B.F.), and cited evidence against any significant intrarenal shunting mechanism.

MUNCK [44] has studied six patients with oliguric failure, measuring the R.B.F. after inhalation of 85-krypton and renal-vein catheterisation, and the G.F.R. by means of creatinine clearance. He found that, whereas the R.B.F. was reduced to about a third of normal, the G.F.R. fell 1% or less, suggesting that some mechanism other than simply reduced blood-flow was at work. In this connection there has been a valuable report by GRABER and SEVITT.[45] They studied renal function in seventeen severely burned patients, and in the eleven fatal cases attempted to relate the functional effects to structural changes in the kidneys. Several points of great interest emerge. The development of azotæmia was generally related to age: the older the patient, the more likely was azotæmia. Secondly, azotæmia developed in some patients without a phase of oliguria. Thirdly, persistent tubular activity was found whether or not azotæmia developed. In two cases severe azotæmia was observed in the absence of tubular necrosis. Fourthly, in all patients the G.F.R. decreased in the first twelve hours after burning. In some patients (mostly children) this decrease was temporary, persisting for twenty-four to seventy-two hours; in others (the older ones and those most severely burned) no such recovery took place. Similar functional variation has been reported in burned goats.[46] Fifthly, fatty droplets appeared in the cytoplasm of the epithelial cells of the glomerular tuft, and the severity of this change, the G.F.R., and the degree of azotæmia were interrelated; but this interrelation did not extend to tubular changes. These striking findings must surely indicate that the azotæmia which develops in severely burned patients is a consequence of glomerular changes, and cannot be wholly accounted for by tubular necrosis or altered R.B.F.—a conclusion that

32. Semple, A. B., Davies, J. B. M., Kershaw, W. E., Hill, C. A. St. *Brit. med. J.* 1954, i, 1002.
33. Rawal, B. D. *Trans. R. Soc. trop. Med. Hyg.* 1957, **53**, 61.
34. Cathie, I. A. B. *Lancet*, 1954, ii, 115.
35. Scriver, W. de M., Oertel, H. *J. Path. Bact.* 1930, **33**, 1071.
36. Dunn, J. S., Montgomery, G. L. *ibid.* 1941, **52**, 1.
37. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., Prichard, M. L. Studies of the Renal Circulation; p. 142. Oxford, 1947.
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39. Bywaters, E. G. L., Dible, J. H. *J. Path. Bact.* 1942, **54**, iii.
40. Lucke, B. *Milit. Surg.* 1946, **99**, 371.
41. Bull, G. M., Joekes, A. M., Lowe, K. G. *Clin. Sci.* 1950, **9**, 379.
42. Darmady, E. M. *Brit. med. J.* 1950, i, 1263.
43. de Wardener, H. E. *Lancet*, 1955, i, 580.
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45. Graber, I. G., Sevitt, S. *J. clin. Path.* 1959, **12**, 25.
46. Dzieman, A. J. *Fed. Proc.* 1948, **7**, 29.

may be correct also of azotæmia associated with tubular necrosis due to other causes, though clearly further work is needed on this point. Certainly very slight histological changes in the glomeruli can give rise to considerable alterations in function, and the light microscope may not suffice for observation of the glomerular epithelium.

The cause of the glomerular changes observed by GRABER and SEVITT is unknown. An obvious possibility is renal vasoconstriction, either general or local—a shunting mechanism in fact. (There is no lack of circulating vasoconstricting substances after burning; and the fact that the blood-pressure initially remains normal despite decreased cardiac output may reflect their activity.) Another possibility, mentioned by GRABER and SEVITT, is impaired G.F.R. from therapy-induced hyperproteinæmia (8–9·5 g. per 100 ml.) in patients who have received infusions of plasma containing 5 g. protein per 100 ml. Whatever the cause, these observations are of great interest. Can it be that the uræmia of acute tubular necrosis is really due to glomerular damage?

Sickness in Office

" When beggars die, there are no comets seen—
The heavens themselves blaze forth the death of princes."

In the same way the organs of mass information today blaze forth the illnesses of national and political leaders, sometimes with a wealth of medical detail which English doctors find surprising. Yet Press and public interest in the health or sickness of men in great positions does not come of vulgar inquisitiveness only: it contains a real element of sympathy and a still more evident element of anxiety. In Britain custom has long established that public anxiety about the health of the Sovereign is legitimate, and ought to be satisfied where there is any real threat to life or capacity. The illness which impaired the judgment of GEORGE III had its political consequences; and so no doubt have innumerable other illnesses throughout history. Today such possibilities have acquired greater importance because of the intensity of the pressure on the men at the top, and because of the gravity of the decisions which some of them are in a position to take. It is this that makes people increasingly troubled about the health of rulers, and has evoked suggestions that not only their entry to office but also their tenure of it should depend on their physical and mental fitness as judged by medical criteria.

For reasons discussed in the Socratic dialogue on p. 882, the advanced society of today generally entrusts high responsibilities to leaders who are well advanced in age; and it must therefore expect them to have the occasional or even permanent disabilities of their time of life. Their capacity for activity will obviously be lower than in youth; but, when it was argued against FRANKLIN ROOSEVELT'S first candidature that his disability made him " inactive ", most people would have accepted his retort that he was offering himself as President not as an athlete. Nor should one forget that few reach high political office nowadays without having quite exceptional stamina: and one reason why such office is entrusted to them by those who know them is that over and over again, in the tests of earlier life, they have been found to act reliably and in character, even if tired or unwell. Such men, who have deservedly won confidence, can be hard to replace; and when at times they show illness or strain the usual practice is to lighten their load and allow them to carry on as long as they can. But of course, like so many other sensible arrangements, this carries a risk—the risk that loyalty and respect will encourage the leader to continue when his judgment is really impaired—when he is in fact no longer the person who was chosen.

All illness affects judgment to some extent; and so may mere fatigue, or pain, or mental distress. At some time in his life every doctor faces this problem in a personal form—in deciding whether he is fit to operate with toothache, and whether his patients will take more harm from his absence than from his presence at intellectual and mental half-pressure. It has been held by the courts that a surgeon who, knowing himself a dying man, with whatever emotional and other consequences that realisation involves, yet continued to operate was not thereby neglecting his duty. The value of his skill and experience might outweigh the possible lowering of his efficiency by his illness; and presumably this holds good for larger matters of life and death. At the same time, misgivings are bound to increase in proportion to the danger from misjudgment: it has never before been possible for a miscalculation, a mishearing, or a frank delusion, in one of quite a number of places, to reduce human life to perhaps a few scattered remnants. Probably the risk that physical illness will render an old man's judgment less objective is no greater than the risk that the stresses of private life will disturb the judgment of a younger man. Against these risks, as against the greater (though rarer) risk of incipient psychotic illness, at any stage of life, in a powerful leader, the only real safeguard is a sharing of power—a system of checks and balances in which nobody's word is sovereign without his colleagues' scrutiny. In such sharing of responsibility we should have fuller confidence if we did not know that the people who achieve most power are commonly men of unusually forceful personality, or high prestige, whose word will often prevail for a time even against facts. Unhappily, we need not go back more than thirty years for an extreme example of successful psychopathic leadership.

If it became customary to refer such problems for medical adjudication, we should not envy the adjudicator. What terms of reference could he have? How can one estimate the value of a leader without being influenced by one's own opinion of his opinions? Decisions on fitness to rule must still, we fancy, be left to the people closely concerned, among whom a special responsibility rests on those who have observed, as friends and associates, the ups and downs that form the life of everyone, high or low. All that the public can do to prevent dangerous aberrations is to refuse the rule of autocrats.

Annotations

FROZEN SECTION

THE purpose of a frozen section is not to make a diagnosis: it is to arrive at a therapeutic decision. An exact histological and even cytological description is often possible and always satisfying; but it is never necessary. More often than not all that needs to be decided is whether the lesion is malignant or not. But confusion of purpose is not the only reason why the frozen section still does not occupy what its advocates claim to be its rightful place in surgical diagnosis. Ackerman and Ramirez [1] deplore that the method is still used by some merely "to satisfy the surgeon's intellectual curiosity or to prove that there is a pathologist in the hospital": and the procedure can certainly degenerate into a kind of parlour-game where a team of super-doctors must arrive at histological diagnoses without knowledge of the patients' history or physical signs. That in conscientious and experienced hands the examination of frozen sections can provide accurate and useful information was clearly shown by Ackerman and Ramirez. Their material consisted of 727 tumours (611 of which were malignant) and 542 non-neoplastic lesions. The overall accuracy was 98%: they had made 4 false positive and 22 false negative diagnoses.

Apart from possible diagnostic errors and very occasional technical difficulties, tumour implantation is often mentioned as a risk of biopsy. That it can happen is not in doubt: the more one looks for it, the more abundant is the evidence. Whether the risk is great is another matter. It must be exceedingly rare for a previously confined and therefore curable tumour to be converted into an incurable one by surgical dissemination: it seems more likely that the knife (or even more the blunt dissector, the impatient finger, the crudely handled swab, or the capricious sucker) merely opens up additional avenues to intrinsically invasive cells. None the less, precautions can and should be taken; and the possible risks should always be balanced against the potential benefits. Thus, when at operation a doubtful mass is encountered in the cæcum, Ackerman and Ramirez wisely recommend an ileohemicolectomy without preliminary frozen section: the risks of the operation, even if the lesion should prove innocent, are less than the risks of dissemination by biopsy if it should be malignant. On the other hand, despite the danger of tumour implantation, the mortality of a radical pancreaticoduodenectomy is such that the risks entailed in frozen-section biopsy are outweighed by the chance, however remote, that it might exonerate a doubtful pancreatic lesion.

The most common site for frozen-section biopsy is the breast; and in Ackerman and Ramirez' series of 440 sections from breast lesions 263 were tumours. Of these, 205 were malignant. Diagnosis had to be deferred in 10 cases; but the only actual errors were 4 false negatives. To achieve such accuracy a more than perfunctory cooperation between surgeon and pathologist is essential. This is often preached but not so often practised. Many a morbid anatomist who pronounces on frozen sections as part of his daily routine has not set foot in the operating-theatre or ward for years. Such pathologists will often argue (and argue with a grain of justice) that it is the surgeon's task to invite them: it is with the surgeon that responsibility for the patient's welfare ultimately rests, and he knows (or should know) that the accuracy of a frozen-section diagnosis depends in no small measure on the pathologist knowing where the section came from or even guiding the surgeon in his choice. If, however, a few morbid anatomists are all too ready to compromise, the attitude of some of their surgical colleagues is no less curious.

Though microphotographs are still de rigueur for "serious" surgical papers, many authors have not looked down a microscope since student days. This state of affairs would have horrified their masters fifty years ago much as it would horrify surgeons today if somebody suggested that, having ascertained the size, shape, position, mobility, and sensitivity of a lump, they should call in a physicist to tell them whether or not it is fluctuant. The bulk of morbid anatomy is easy: often a glance by a first-year clinical student will give the answer whether the lesion is cancerous or innocent. Why is that glance so rarely cast by surgeons? Perhaps it would dispel the mystique which may be an unacknowledged attraction of the method.

In many sites—such as the thyroid and prostate—Ackerman and Ramirez suggest that frozen-section diagnosis has a wider scope than it is generally given. Their personal experience is impressive; but perhaps they underestimate the confusion in nomenclature which, in most hospitals, still bedevils clinicopathological collaboration. Often what is cancer to the pathologist is not cancer to the clinician—and sometimes what is cancer to both is not cancer to the patient. Pathologists are becoming increasingly aware of grades of biological malignancy which do not necessarily correspond to histological malignancy and which they are yet unable to express. To most clinicians, on the other hand, "cancer" still spells doom unless radically treated; and to most patients in this country it spells doom unqualified. In the American series the discrepancy between the numbers of false negatives and false positives may be significant. On a-priori grounds there is no valid reason for this difference: if the conscientious pathologist will think twice before passing sentence of malignancy, he will be equally reluctant to jeopardise the patient's chances of cure by undue optimism. Whereas death from malignant spread, however, can incontestably prove a negative diagnosis false, a positive diagnosis is not easily disproved. Cancer may be diagnosed on a frozen section from the prostate and confirmed on the radical-operation specimen. This still does not necessarily mean that, had it been left behind, it would have shortened the patient's life by a single day.[2] The number of false positives may thus be higher than statistics suggest.

ERRORS IN DIETARY CONTENT

STANDARDISATION of diets with particular reference to their electrolyte content has become increasingly important in investigation and treatment. Whereas diets were once defined in the most general terms such as "low fat" or "high protein", considerable precision is now implied by "diet to contain 10 mEq. (or less) of sodium daily". Yet in aiming to be so precise we may be deceiving ourselves; for what is ordered is not necessarily what the patient actually eats. Day-to-day variation in the constituents of a constant diet has previously been reported [3 4] but has largely been ignored in recent years.

In a timely investigation Flear et al.[5] have analysed the sodium, potassium, and chloride content of two diets (provided for balance studies), and compared their results

1. Ackerman, L. V., Ramirez, G. A. *Brit. J. Surg.* 1959, **46**, 336.

2. See *Lancet*, Feb. 21, 1959, p. 398.
3. Bassett, S. H., Van Alstine, H. E. *J. Nutr.* 1935, **9**, 175.
4. Word, A. H., Wakeham, G. *Univ. Colo. Stud.* 1938, **25**, 181.
5. Flear, C. G. T., Hughes, P., McLellan, A. *Brit. J. Nutr.* 1959, **13**, 54.

with those found by calculation from tables.[6] They have similarly examined a standard "low-sodium" diet designed to supply 10 mEq. or less of sodium daily. The work is of a high order; many samples were analysed, and a method was used whereby dry ashing was avoided. The results are startling in their variety. In the two diets for balance studies, calculation gave a mean 13·5% deficit for sodium, a 10·4% excess for potassium, and a 1·4% excess for chloride. Even more striking were the so-called low-sodium diets, which contained 50·5–326·0% more sodium than was intended.

Several factors contribute to such errors. Probably the most important is lack of care in preparing the food. A more subtle variable is the mineral content of the raw materials.[7] How can these errors be avoided? For balance studies one dietitian might prepare a large sample of food which would be kept at a low temperature and from which all meals throughout an individual study would be taken; but this would be expensive and inconvenient and not many patients would be readily induced to eat the same amount of the same diet daily for several days or weeks. Improvement of therapeutic diets would call for more hands, and so for more money. Probably we must make do as best we can with what we have. But we should not take too sanguine a view of the patient's chances of receiving precisely the diet we precisely prescribe.

FRACTURES OF THE FINGER

FRACTURES of the finger form a major part of the work of any casualty department. The disability which follows these injuries is often considerable, and work may be impossible because of a cumbersome splint.

Injuries of the distal phalanx usually unite readily, and the bony damage is often best ignored. Simple protection of the finger-tip and treatment of the soft-tissue injury, which may require removal of the nail, will usually enable the patient to work throughout the period of treatment. Where the fracture involves the base of the phalanx and goes into the joint the prognosis is less good, but treatment must again be directed towards early restoration of function. If the fracture involves the insertion of the flexor or extensor tendons the finger should be immobilised for a short period, with the affected tendon relaxed.

In undisplaced fractures of the middle phalanx immobilisation is hardly necessary. Commonly, however, these fractures lie transversely and are displaced anteriorly by the pull of tendons. It may be difficult to reduce the fracture and hold its position in plaster, and sometimes the finger has to be immobilised with its neighbour to maintain the position of the fragments; traction should not be necessary. A convenient method of reduction, using a padded metal splint, has been described by Burnham.[8] In this method the splint is applied in the desirable position, and the fracture is subsequently reduced onto it. Padded splints of this type are a convenient means of treating many finger injuries, and are often more comfortable and more adaptable than plaster.

In the proximal phalanx the neck of the bone is often involved, and this fracture must be treated in acute flexion if reduction is to be maintained. Some of these injuries require open reduction and fixation with a wire, but the dangers of joint stiffness after this type of intervention are very great.

Immobilisation following phalangeal fractures need never be lengthy, and complete immobilisation for more than three weeks will often produce a stiff and useless finger. The disability which follows these injuries is due to disturbances of soft tissue rather than to the bone injury itself. Unfortunately these disturbances are as often attributable to the treatment as to the injury.

OPERATIONS FOR ISCHÆMIC HEART-DISEASE

IN the past two years[1] there has been no striking advance in the surgical treatment of ischæmic heart-disease; but much clinical and experimental work is being carried on, particularly in the United States. A report by Longmire et al.[2] suggests that direct-vision coronary endarterectomy is feasible in some cases of angina pectoris. By removal of thrombi and atheromatous plaques from the diseased vessels, this operation satisfies the surgical principle of relieving obstruction whenever possible; and it also increases the total blood-flow to the myocardium, unlike the Beck procedure which provides a balanced distribution of blood through the production of intercoronary anastomoses. But endarterectomy is technically more difficult, and the operative risk may be greater. Longmire et al. make no extensive claims but merely report the short-term results in 5 cases; 1 patient died during the operation, but anginal pain was abolished or greatly relieved in the 4 survivors. Since the longest follow-up period was only nine months, no conclusion can be drawn as to the long-term effect. The success of endarterectomy depends on the arterial tree being patent distal to the obstruction, and whether this is usually so in anginal patients is open to doubt. Longmire et al. believe that the occlusive process is likely to be concentrated near the origin of one or more of the main coronary vessels and that the distal parts are relatively free—conclusions based upon the well-known postmortem studies of Blumgart et al.[3] and the coronary arteriographic experiments of Cannon et al.[4] In their cases Longmire et al. observed brisk retrograde flow after removal of the thrombi, which they regarded as further evidence of patency of the remainder of the system.

An entirely opposite view is expressed by Thal et al.[5] as a result of coronary arteriography. Elsewhere in the body—in the brain, abdominal aorta, and peripheral arteries—arteriography has become almost commonplace. Since 1945 arteriography of the coronary arteries has occasionally been described,[6–8] but this particular circulation has remained largely in darkness owing to the technical problems and to the risk of producing arrhythmia and myocardial damage. Thal et al. have now undertaken coronary arteriography in 50 patients without ill effect. A catheter is passed into the aorta from the brachial artery under local anæsthesia and the tip positioned one inch above the aortic valves; by means of a mechanical syringe synchronised with an electrocardiograph the injection is completed during one cardiac cycle and films are exposed in two planes in rapid succession. This work suggests that in angina diffuse disease of the coronary circulation is the rule and segmental blockage the excep-

6. McCance, R. A., Widdowson, E. M. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1946, no. 235.
7. McCance, R. A., Widdowson, E. M., Shackleton, L. R. B. *ibid.* 1938, no. 213.
8. Burnham, P. J. *J. Amer. med. Ass.* 1959, **169**, 663.

1. See *Lancet*, 1957, i, 1025.
2. Longmire, W. P., Cannon, J. A., Kattus, A. A. *New Engl. J. Med.* 1958, **259**, 993.
3. Blumgart, H. L., Schlesinger, J. J., Davis, D. *Amer. Heart J.* 1940, **19**, 1.
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5. Thal, A. P., Richards, L. S., Greenspan, R., Murray, M. J. *J. Amer. med. Ass.* 1958, **168**, 2104.
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7. Pearl, F., Gray, N., Friedman, B. *Ann. Surg.* 1950, **132**, 959.
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tion; Thal et al. found segmental blockage in only 2 of their patients, and consequently they believe that endarterectomy is unlikely to succeed.

Divergent opinions such as these are difficult to reconcile; but from coronary arteriography, if it proves as trouble-free and informative in other hands, more can probably be learnt about the lesions in ischæmic heart-disease. If observations elsewhere in the body are a guide, it seems likely that both localised and diffuse disease will be found in individual patients, and call for different operative approaches.

While these questions are being settled the Beck operation continues to give good results at Cleveland.[9] In 1954–58, 347 patients were operated on with a mortality of 6% overall, and of 2% in the last 200 cases. 295 patients are still alive, and the result is described as excellent or good in no less than 94%—a striking figure. But the follow-up period in many is still short, and the longest is only four years, so the ultimate results in terms of increased survival are still unknown. If, as Blalock [10] has suggested, the results are very similar after different operative procedures, perhaps the production of inter-coronary anastomoses is the factor common to each; and in this case there is much in favour of undertaking the simplest and safest operation. The further outlook in the surgery of ischæmic heart-disease is clearly unsettled.

SUCCESSFUL KIDNEY HOMOGRAFT

THE Peter Bent Brigham Hospital, Boston, Mass., has announced what appears to be the first successful kidney homograft in non-identical twins. A man, aged 23, had chronic glomerulonephritis with severe uræmia and hypertension; his life expectancy was thought to be a matter of days. He was given whole-body irradiation in two doses—250r followed eight days later by 200r. No corticoids were given and no bone-marrow graft was attempted. A kidney from his twin brother was transplanted on Jan. 24, and both diseased kidneys were later removed. For a month after the irradiation he was kept in a room sterilised by detergent, with positive-inflow ventilation and an ultraviolet-ray barrier. The patient is now in good health, and the kidney seems to be functioning well; the blood-pressure is normal, and the blood and urine show no evidence of uræmia or bone-marrow damage.

Survival for three months does not prove complete success, for in the past kidney homografts from unrelated persons have functioned for as long as five months before rejection; but none functioned as rapidly or efficiently as in the present case. The donor is thought to be close genetically to the patient (his blood-groups are identical); but he is not an identical twin because his appearance differs, and a skin-graft from the patient to him was rejected. Three factors are thought to have contributed to the success: the genetic closeness (though not identity) of the brothers; the severe uræmia, which depressed immune mechanisms; and the divided doses of radiation, which were enough to depress immune reactions without completely destroying the bone-marrow.

Successful kidney transplants in identical twins have previously been reported from the Peter Bent Brigham Hospital [11]; but this case, of a successful homograft to a patient not genetically identical with the donor, is apparently unique.

9. Beck, C. S., Leighninger, D. S., Brofman, B. L., Bond, J. F. *J. Amer. med. Ass.* 1958, **168**, 2110.
10. Blalock, A. *Lancet*, 1958, i, 1013.
11. Murray, J. E., Merrill, J. P., Harrison, J. H. *Ann. Surg.* 1958, **148**, 343; see *Lancet*, Jan. 3, 1959, p. 31.

EXPANSION OF CANCER RESEARCH

IN about two years, when its new building in Lincoln's Inn Fields is ready, the Imperial Cancer Research Fund will be able to expand its work greatly. Prof. G. F. Marrian, F.R.S., who is to take up his full duties as director of research next October, is already making plans for this expansion, in which the laboratories are to be organised in divisions—though in practice, of course, most research problems will need an interdivisional approach.

The division of experimental biology and virology has already been established in the Fund's laboratory at Mill Hill, headed for the past six months by Mr. R. J. C. Harris, PH.D., who was formerly in charge of the Pollard's Wood division of the Institute of Cancer Research. The division of pathology will be temporarily housed at 48, Lincoln's Inn Fields, where Dr. A. R. Currie, of Glasgow, will take up his appointment in October. The nucleus of a division of physiology and endocrinology already exists at Mill Hill, and so far as space allows it will be encouraged to enlarge, under the leadership of Mr. P. C. Williams. The division of biochemistry and chemistry, to be established in October under the leadership of Professor Marrian, has a nucleus at the Royal College of Surgeons and will have further accommodation at 48, Lincoln's Inn Fields until it can move into the new building. Dr. C. C. Spicer, of the Public Health Laboratories at Colindale, is to head a small division of statistics. Dr. James Craigie, F.R.S., having given up his administrative work as director of the Mill Hill laboratories, remains on the research staff of the Fund.

The 56th annual report,[1] presented on Wednesday, contains a brief account of the work of the clinico-pathological research unit at Lincoln's Inn Fields, written by Prof. Geoffrey Hadfield, its director, in terms readily intelligible to the general reader. This report, illustrated by photographs, is again designed to attract and maintain the interest of the Fund's lay supporters.

At £260,000 the income in the year ended last November, from all sources except legacies of £1000 or more, was nearly £40,000 higher than in the previous year; and about £138,000 was from subscriptions and donations, including charity performances. Legacies, at nearly £280,000, increased by some £50,000.

CARDIAC SURGERY TEAM TO VISIT MOSCOW

Mr. W. P. Cleland, Dr. D. G. Melrose, Mr. H. H. Bentall, and four other members of the Postgraduate Medical School of London's cardiac surgery team have left for Moscow where they are to demonstrate the clinical use of the Melrose heart/lung machine, the technique of elective cessation of the heart-beat, and British methods of open intracardiac surgery.

The operations are being undertaken at the invitation of Professor Bakulev, president of the Academy of Medical Sciences of the U.S.S.R., in the Institute of Thoracic Surgery. During their stay in Moscow the British team will be the guests of the Soviet Government. Transport expenses are being met by grants from the British Council, the Nuffield Foundation, the Postgraduate Medical School, and the boards of governors of Hammersmith, King's College, and the Brompton Hospitals. A Melrose machine has been purchased by the Russian Government for use in Moscow, and will be used during the demonstrations. Anæsthetic equipment and drugs and surgical instruments have been supplied for the demonstrations by British firms. The team expects to spend two or three weeks in Moscow, and some 8 or 10 operations have been planned.

Dr. A. C. ALPORT, formerly professor of medicine in the University of Cairo, died in London on April 17 at the age of 79.

1. From the office of the Fund at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

Special Articles

HARLOW INDUSTRIAL HEALTH SERVICE

Lessons of an Experiment in Industrial Cooperation

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MEDICAL DIRECTOR OF THE SERVICE

Introduction

THE Harlow Industrial Health Service is the third phase in the creation of a model health service for the new town of Harlow. The two earlier phases—the building of five general-practitioner health centres, the Essex county general and special clinics, and the temporary hospital outpatient department—have already been described.[1 2] In this phase, as in the previous ones, the initiative as well as the necessary capital came through the forward-looking generosity of the Nuffield Provincial Hospitals' Trust.

Many people are apt to look on health services in industry as a medical luxury, comparatively low in the scale of priorities as compared with hospitals, specialists, and general practitioners. This view is understandable, whether or not it is justified. Thanks to the fine work of the Factory Inspectorate, both lay and medical, most of the conventional industrial diseases have been decisively defeated. Underemployment of industrial nurses in some factories has led to complaints of uneconomic use of our limited nursing force, at a time when the needs of hospitals and district nursing services are greater than ever before. Finally, it is sometimes said that factory medical departments are duplicating unnecessarily the work of the hospitals and general practitioners.

These are points of substance. But when they are examined closely, they are found to arise either from faults of existing organisation or from an imperfect appreciation of what goes on in the factories and other workplaces of Great Britain.

The defeat of conventional industrial disease is a containing operation, successful only because precautions are maintained. Moreover, it is still far from complete, especially where respiratory disease is concerned. Industry today is constantly introducing new processes and new substances, each of which may bring with it new and often unsuspected risks. New applications of radioactivity and chemical technology are cases in point. Nor is the speed of change likely to slacken in the future. Again, the risks and stresses of work often play an important part in the production of gastric, cardiac, neuromuscular, and pyschological illness.

From a non-medical viewpoint, of an even greater importance in the national picture is the enormous loss of production caused by ill health. In terms of days lost per annum, ill health is many times more important than industrial disputes (280 million days in 1954–55 as compared with $3^3/_4$ million).[3] In terms of loss of national output, ill health probably costs the nation between £800 million and £1000 million per annum.[4] Later, I shall suggest that the establishment of a comprehensive industrial health service on a national basis might involve a non-recurring capital expenditure of £30 million and an average running cost to industry of £1 10s.–£2 per employee. Such a service has only to save one-twentieth of the productive time lost through ill health each year to pay for itself. Whatever it does beyond this is, in terms of simple economics, a bonus for us all.

Though prolonged absence from work is almost always due to serious illness, physical or psychological, this accounts for only about half of the total working time lost. The rest of the time lost is due to minor or ambulatory ill health, much of which can be properly dealt with at work. Thus Schilling and Roberts [5] showed that the starting of an efficient medical department in an engineering works employing 850 people cut the time lost, as shown by doctors' certificates, by as much as a half. This took no account of the loss for under-four-day periods for which no doctors' certificates were needed. The explanation is not hard to find. Most people want to work if they can safely do so. Attendance at a doctor's surgery often means loss of half a working day. Ten minutes in the factory medical department or industrial health centre is a common-sense alternative, always provided that proper relations with the general practitioners are maintained. Again, prompt and efficient treatment of minor trauma reduces the risk of sepsis.

These facts are sufficiently obvious for most large industrial concerns, including many shops and offices, to think it worth providing their own medical departments. As a result, something under half the workers of Britain now get some kind of medical cover supplied by the employers. In 1948, of the 4884 factories with over 250 workers, 2018 had medical services of their own; the proportion is much higher in factories employing over 1000 workers. By contrast, of the remaining 238,885 factories with less than 250 workers, only 2481 had medical services.[6] The explanation is one of simple economics. A trained State-registered nurse costs £650 per annum, and perhaps another £350 per annum in drugs, dressings, and other supplies. This is an impossible overhead for the small factory. Moreover, the nurse in the factory with less than 100 workers—and about 230,000 of our factories come into this class—will be grossly underemployed. Indeed, a full-time nurse is probably unjustified in any factory with less than 250 workers, and in many factories with between 250 and 500 workers. It is in such factories that criticism of underemployment of nurses may have substantial justification.

If the small and medium factories are to have their legitimate needs economically and efficiently met, the only practical answer is for a number to combine together. This is easy enough to say, but extremely difficult to do. What follows is an account of how one such combined

1. Taylor, C., et al. *Lancet*, 1955, ii, 863.
2. Bach, H. E., et al. *ibid.* 1958, ii, 1055.
3. Reply by the Minister of Labour, *Hansard*, June 14, 1956. The Minister pointed out that the figure for ill health excluded absence of less than four days, and that for industrial disputes excluded stoppages involving fewer than ten workers. The figure for ill health remains fairly stable from year to year (Ministry of Pensions and National Insurance Digest of Incapacity Statistics), but the figure for industrial disputes fluctuates considerably.
4. This overall figure has been calculated on the following basis. The total population in civil employment in 1956 was 23 million. The gross national product was £18,000 million. So the gross national product per person in civil employment was about £780 per annum. Assuming a 280-day working year, the loss from 280 million working days is about £780 million. But this makes no allowance for sickness absences of less than four days.
   This crude calculation gives no more than an indication of the order of the figures involved. Even the higher figure of £1000 million may well be an underestimate.
5. Roberts, M., Schilling, R. S. F. *J. industr. Nursing*, 1952, **4**, 69.
6. The Functions of an Occupational Health Service in an Industrial Organisation. Association of Industrial Medical Officers. 1956.

industrial health service has been built. The main pattern follows fairly close to that of the Slough Industrial Health Service, pioneered by Dr. Austin Eagger.[7] But the conception is in some ways different and the scale is rather smaller. This may make the Harlow Industrial Health Service an easier model for others to follow.

The General Picture

In 1954 the Nuffield trustees suggested the creation of an industrial health service, to meet the health needs of the factories on Harlow's industrial estates. This necessitated the voluntary cooperation of at least a majority of the town's industrial employers. They had to be satisfied that the conception was sufficiently practical and useful for them to pay substantial subscriptions to keep the service going over the years ahead. A scheme had, therefore, to be prepared which would meet their needs and was at the same time financially sound.

The generosity of the Nuffield trustees enabled me to devote about a year to the preliminary survey, planning, building, and recruitment of firms and staff. The importance of this preliminary phase cannot be overemphasised. It is an initial cost which must be faced before any return whatever can be received. Allowing for a part-time salary, secretarial help, and travelling, it may be estimated to have cost £2000. The experience gained at Slough and Harlow may enable future schemes to be prepared more quickly. But in view of the necessary factory visiting and the meetings which have to be called, the preparatory period cannot be drastically cut.

Formation of the Service

Six separate moves had to be made, the first four being carried out simultaneously:

1. *Introduction to the Harlow Industrialists*

In November, 1954, Mr. Farrer-Brown, then secretary of the Nuffield Trust, addressed a lunch-time meeting of the employers and invited them to visit Slough to see what had been done there. In January, 1955, a party of Harlow employers were shown the Slough Industrial Health Service in operation. They were addressed by Dr. Austin Eagger and by two Slough employers.

Next, the Harlow Industrial Employers Group set up a subcommittee, and this later initiated the legal steps necessary to set up a non-profit-making charitable company on Slough lines. By June, 1955, plans were far enough advanced for a full meeting of industrialists to be called to appoint a solicitor and an auditor and to bring the company into existence.

2. *Survey and Costing of Existing Services*

Eight industrial medical departments and services were visited in different parts of the country. Employers and industrial medical officers gave every facility to enable their work to be described and costed.

The study of the Slough Industrial Health Service was of special value: I approached Slough in sceptical mood, but left it converted. But in certain respects, Slough is not typical of industrial Britain. The town of Slough lacks a full hospital service. In consequence, the Industrial Health Service has to supply certain facilities, such as major X-ray equipment, which would normally be available in regional-board premises. Moreover, the service includes a fine rehabilitation unit at Farnham Park, which serves not only Slough but also the whole hospital region and places even further afield. In consequence, the service can legitimately expect and receive a regular grant income from the regional board.

In calculating costs, it was assumed that Harlow would have a hospital in about six years' time, and that the statutory health authorities would be meeting all their obligations. An industrial health service would not have any rehabilitation beds of its own; nor would it duplicate the proper functions of a hospital outpatient department.

The conclusion reached was that efficient but not luxurious service for 10,000 or more workers might be expected to cost £15,000 per annum, or 30*s*. per head.[8] With fewer workers, the cost would be proportionally higher and with more workers it would be proportionally lower.

3. *Visiting and Survey of Harlow Factories*

All factories employing more than 100 workers and many of the smaller factories were visited. At each factory, the degree of interest was assessed, existing first-aid facilities were examined, and the work done, the hazards involved, and the accidents and sickness-rates were inquired into. A detailed report on each factory was prepared. These reports were again of great value when doctors were being introduced to the factories they were to look after.

In gaining the cooperation of managements, it is important to reach the level at which decisions are actually taken. In smaller factories, the owner or managing director is usually available in the factory itself. But many larger factories are branch establishments of nation-wide organisations. While the good will and cooperation of the location and personnel managers are essential, final decisions are often taken at board meetings in London. So one may have to seek out chairmen and managing directors far away from the scene, before participation is finally achieved. Personal introductions are a great help. The kindness, patience, and hospitality of higher management, both on location and at head offices, has been striking. But the time taken in recruiting a single major factory may be considerable.

4. *Planning, Costing, and Organisation*

We were advised that our first object should be an efficient treatment service, and our experience has confirmed that the first requirement of both management and workers is that injury or illness in the factory should be promptly and efficiently treated. When this has been done, the confidence and good will which are built up provide a background against which advice on prevention is acceptable.

It is all too easy for the doctor entering industry for the first time to assume an omniscience which is quite unjustified. Management involves many skills of which doctors know little or nothing. Bluff on the part of the doctor is quickly detected. But honest confession of ignorance and willingness to find out are equally appreciated. In the process of finding out about the many specialised problems of industrial medicine, the members of the Association of Industrial Medical Officers have provided a well-informed and extremely helpful panel of expert knowledge.

An efficient treatment service for a group of factories has four levels:

1. First-aiders on the factory floor.
2. Industrial nurses, available when needed in the factory first-aid or medical department.
3. A headquarters, hereinafter called the Industrial Health Centre, continually staffed by at least one industrial nurse, where full treatment facilities can be concentrated.
4. Industrial medical officers, available regularly daily at the Industrial Health Centre, and when needed in the factories.

Mobility of nurses and doctors is an essential, to which firms rightly attach great importance. They want immediate help in emergency, and regular treatment with a minimum loss of working time. At Slough, the needs of the smaller firms are met by a complete mobile surgery. At Harlow, all but the smallest factories have their own first-aid rooms. It was decided therefore that a mobile surgery was unnecessary, but that a nurse should do a daily factory round, running a short clinic in each first-aid room at a regular time.

7. Eagger, A. Slough Industrial Health Service. Annual reports nos. 1–11 (1947–58).

8. Details of costs of a number of industrial medical departments are given in the report of the Association of Industrial Medical Officers (ref. 6).

At these clinics repeat dressings and non-urgent cases are dealt with. At other times, trivia are dealt with by the first-aiders trained by the service, using boxes stocked by the service to a level somewhat above the Ministry of Labour's statutory requirements; non-trivia are referred to the centre, or are dealt with by emergency visits. At first, the nurses did their rounds by bicycle, using a district nurse's bag. Soon a small Morris station wagon was acquired; later, this was supplemented by a Bedford 'Workabus,' in which a patient can be transported lying down; both vehicles carry stocks for first-aid boxes and also serve to transport patients needing suture, for example, to the industrial health centre. In our experience one nurse and one vehicle can satisfactorily look after upwards of twenty factories employing 1500 or more workers. The nurses themselves drive the vehicles.

After careful thought, it was decided to make use of general practitioners as visiting medical officers on a sessional basis, rather than to employ any full-time industrial medical officers. Though this has made the administration more complicated, experience has amply justified the decision. The practitioners of Harlow all work in groups, and at least one member of each group has wanted to play a part in the service. So a complete twenty-four-hour cover has been possible, using at first eight (and later ten) visiting medical officers. A session extends from 9.30 A.M. to 1.30 P.M. or from 1.30 P.M. to 5.30 P.M. During each session a visiting medical officer must visit the Centre once at a prearranged time, also one or more factories (on a rota); for the rest of the session, he or a substitute provided by him is on call for emergencies. Night cover (from 5.30 P.M. to 9.30 A.M.) and weekend cover for emergencies is provided by two of the younger practitioners, member factories being notified monthly of who is on call.

The doctors are paid at British Medical Association rates, each session being treated notionally as lasting two hours. On this basis, the cost of employing the eight visiting medical officers is £2325 p.a. This is more than the cost of one full-time medical officer, but substantially less than the cost of two, especially if car allowances, superannuation, and National Insurance are borne in mind.

The gains to the service from the employment of general practitioners are considerable. The Harlow doctors already run the principal local-authority clinics. As a result of their industrial activities, they now look after their patients at work as well as at home. They are thus providing a virtually complete extrahospital service. It was feared there might be an impossible division of loyalties; but in practice contact with employers has been entirely to the patients' advantage. Moreover, because many employers live in Harlow, they are patients too. Arrangements for suiting work to the needs of the recovering patient have become realistic; the doctors now know at first hand what the factories can offer.

A further advantage of the employment of general practitioners is that a great deal can be done towards matching management and doctor. Each firm has its own individuality, and experience has shown that managements vary in their attitudes to the personality and methods of work of the doctor allotted to them. By ringing the changes, when appropriate, all-round satisfaction can usually be achieved.[9]

9. Details of the work and conditions of employment of general practitioners as visiting medical officers in the service have already been described. (Taylor, S. *Practitioner*, 1958, **181**, 133.)

The letters of appointment of the doctors have been very carefully drawn, so that their clinical freedom and autonomy is safeguarded, and so that there is no overlap with their duties as general medical practitioners in the National Health Service. The medical director has certain reserve powers, but in practice these have never been used; moreover, all practitioners have the right of appeal to the council of the service.

To avoid overlap, the family doctor is always informed of anything more than the smallest health incident. This works both ways. A family doctor who sees an industrial patient requiring dressings or injections can arrange for these to be given by the service, thus saving loss of working time. To safeguard lists, while preserving free choice of doctors, all visiting medical officers have agreed that if they see a patient industrially they shall not take him on to their list for at least six months. This is in line with the practice adopted in most emergency rota schemes run by practitioners.

To keep down expenses, it was decided that the rest of the staff—the medical director, the secretary-administrator, and the clerk-typist—should be part-time. Apart from the nurses, the only full-time employee is a receptionist-telephonist.

The industrial health centre is open from 7.30 A.M. to 5.30 P.M. Because of factory rounds, the minimum nursing cover needed is two. It was realised that at the start there was bound to be some underemployment of nurses. This righted itself during the first two years, and three additional nurses are now regularly employed part-time.

Three of the larger firms already had their own full-time factory nurse before the service came into being. The service provides them with continuous medical cover and their own visiting medical officers, also holiday and sickness nursing cover, nursing assistance at rush hours, and the special facilities available at the industrial health centre. A fourth firm, employing 450 workers, has given up its full-time nursing orderly, his place being taken by two one-hour sessions by our nurses in the factory medical department, supplemented by the industrial health centre; this arrangement meets fully the factory needs and works to the satisfaction of all concerned.

Detailed estimates of income and expenditure over the five-year period 1955–60 were prepared in advance (table I).

TABLE I—INITIAL ESTIMATE OF INCOME AND EXPENDITURE 1955–60

—	Estimated subscription income (£ p.a.)	Estimated expenditure (£ p.a.)	Annual deficit (£ p.a.)	Cumulative deficit (£)	Nuffield donation (£)
1955–56	6000	9853	−3853	−3853	18,000
1956–57	8000	13,620	−5620	−9473	
1957–58	10,500	15,040	−4540	−14,013	
1958–59	12,500	14,840	−2340	−16,353	
1959–60	15,000	15,150	−150	−16,503	

The estimates of expenditure had to be comprehensive. Besides wages and salaries, National Insurance and superannuation, the following items had to be estimated: rent, rates, heating, lighting, telephone, stationery, postage, equipment, stores, uniforms and laundry, vehicles, petrol and maintenance, insurance (fire, burglary, and civil action), and contingencies.

As a policy, it was decided to pay the rates recommended by the B.M.A. and the Royal College of Nursing, and to tie all other salaries and wages to equivalents in the National Health Service. This has avoided the endless arguments which would otherwise arise through changes in cost of living. A number of the non-salary estimates could only be conjectural.

On the income side, estimates were far harder to make. It was decided that the subscription-rate must be such that in due course the service could hope to be self-supporting. This necessitated a subscription of £2 per employee per annum for full members and £1 per employee for firms with their own factory nurse. For half-time employees, defined as those working twenty-four hours per week or less, half rates only are charged.

It was realised that, owing to the gradual build-up of the service, and of industry in Harlow, the service could not hope to be self-supporting for at least four years. To bridge the gap, the Nuffield Provincial Hospitals Trust has made a donation of £18,000, spread over three years. No less important, the Trust, using the Harlow Development Corporation as its agent, has provided the temporary and permanent industrial health centres from which the service has worked. For these, the service pays a rent of 6% of the capital cost, as is paid by the other users of the Trust's premises in Harlow.[10] Without this generous help, both in capital and current income, the service could not have been brought into existence.

Three years of work, from Nov. 1, 1955, to Nov. 1, 1958, have shown that both subscription income and expenditure have been over-estimated (table II).

TABLE II—ACTUAL INCOME AND EXPENDITURE 1955–57

—	Subscription income (£ p.a.)	Expenditure (£ p.a.)	Deficit (£ p.a.)	Cumulative deficit (£)
1955–56	5162	9066	−3904	−3904
1956–57	6690	11,000	−4310	−8214
1957–58	8384	12,463	−4079	−12,389

Although the cumulative deficit, met by the Nuffield donation, is £1624 less than expected, the position is less rosy than it appears from these figures. The service has to expand to cover a second industrial estate now in the course of development, and subscription income is growing too slowly. If self-sufficiency at the present level of service is to be achieved by 1959–60, even after allowing for the natural growth of existing members, firms employing a further 2000 workers must be recruited as full members (or twice that number on a half-subscription basis). This is no easy task, because most of the non-members are comparatively small; moreover, some have been hit by the credit squeeze and the trade recession. At the same time the service must improve existing facilities and provide new ones where appropriate. We have come thus far only by counting every penny, and more money is essential if we are to do all that we should do in the future. Nevertheless, the task before us, though difficult, is by no means impossible.

5. *Formation of the Company*

The decision to form the Harlow Industrial Health Service Ltd., was taken at a full meeting of industrialists, held in June, 1955.

The formation of a non-profit-making company is a legal and not a medical process. Nevertheless, those who start an industrial health service must take great care over the key document, the memorandum and articles of association. The memorandum must be drawn sufficiently widely to cover all that the service may want to do in the future, but not so widely that its purposes are blurred or its charitable and non-profit-making status are endangered. The first four objects of the Harlow Industrial Health Service are set out as follows:

A. To advance the physical and moral welfare of the population by the prevention and cure of occupational diseases and injuries and to promote the general health of workers.

B. To provide services for medical treatment and for the care of sick or injured workers at their places of employment or elsewhere, and for their full restoration to health.

C. To undertake medical and other teaching in occupational diseases and injuries and in the promotion of occupational and environmental health.

10. Up to one-third of the rent is set aside by the Trust for maintenance and improvements of the buildings.

D. To carry out research and investigation into the causes of occupational diseases and injuries and into the means of promoting occupational and environmental health.

The remaining objects are comprehensive routine legal statements of the means which may be used to achieve these objects.

The other part of the document to which special attention is necessary is that portion of the articles of association dealing with membership and the structure and powers of the council of management. Firms become members of the association in order to participate in its benefits. The running of the service is entrusted to a council of management, none of whom may hold any office of profit in the service. The council is not elected directly by its members, but is comprised in such a way as to be representative of those who pay for and use the service, and of various statutory and voluntary bodies concerned with the health services. This has helped to ensure cooperation and to prevent overlap.

Members of the council are nominated by the following bodies:

Nominating body	*Places on council*
Harlow and district industrial employers group	8
Harlow Trades Council	2
Nuffield Foundation	2
Nuffield Provincial Hospitals Trust	2
Harlow Development Corporation	1
Essex County Council (the local health authority)	1
North East Metropolitan Regional Hospital Board	1
Harlow Hospital Management Committee (pending its formation the Epping Hospital Management Committee)	1
Local Executive Council for Essex	1
Harlow Urban District Council	1
Trades Union Congress	1
British Medical Association	1
Up to 4 coopted members.	

The ratio of two local employees to eight employers has been accepted by the local trades council as a fair one, since the entire subscription cost is carried by the employers. A representative of the British Employers' Confederation and of the Perry Watlington Memorial Trust, an Essex Charity, have recently been coopted to the council.

The council meets quarterly and has no standing subcommittees. It has been agreed that the chairman shall hold office for one year; so far, he has always been an industrialist. Non-attenders may, by leave of the council, send observers without the right to vote. It has never yet been necessary to take a vote at a council meeting.

The industrialist members meet without the officers before each council meeting, and each makes himself responsible for contacting a group of member firms to ascertain any complaints or difficulties which may have arisen in the past three months. Thus all members get a formal opportunity every quarter to express their satisfaction or dissatisfaction with the service provided.

At the first meeting of the council, a medical director and a secretary-administrator were appointed. They were given authority to engage staff; and the starting date of Nov. 1, 1955, was fixed.

6. *Initial Training in Industrial Medicine*

In July, 1955, an intensive weekend course in industrial medicine for the general practitioners was held in Harlow.

The chair was taken by Sir Ernest Rock Carling, Dr. Austin Eagger, and Dr. R. F. S. Schilling, and lectures were given on:

The functions of an industrial health service (Dr. N. Macdonald, Lever Brothers).
Examinations in industry (the late Dr. H. Wyers, May & Baker).
Skin conditions in industry (Dr. L. B. Bourne, A. C. Cossor).
Eye conditions in industry (Dr. H. F. Chard, formerly Ministry of Supply).
The prevention of accidents and industrial diseases (Dr. Schilling, then of the University of Manchester).
Treatment services in industry (Dr. G. Andrew, Walls).
Traumatic and orthopædic services in Harlow (Mr. G. Fisk, St. Margaret's Hospital, Epping).
The proposed Harlow Industrial Health Service (Dr. S. Taylor).

Afterwards the lectures were expanded into a booklet, to serve as a guide for the visiting medical officers, and to help to ensure continuity of treatment.

This course did a great deal to stimulate enthusiasm and to establish common policies and agreement. Since then, doctors

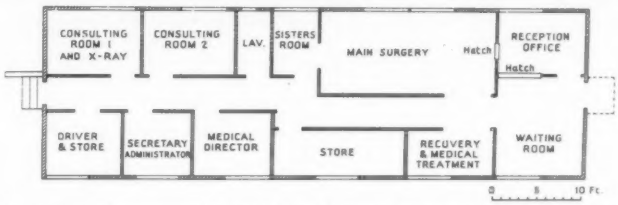

Fig. 1—Plan of temporary industrial health centre, to serve up to 5000 workers. Cost: under £2000 including furniture and equipment.

working in the service have attended refresher courses in industrial medical work at Manchester University, the London School of Hygiene, and the Birmingham Accident Hospital. A meeting has been addressed by medical and lay factory inspectors, and the doctors have themselves addressed the Association of Industrial Medical Officers. Papers circulated to them and to appropriate factory managements deal with specific problems as they arise. Subjects so far dealt with include selenium hazards, cadmium and metal-fume poisoning, noise in factories, trichlorethylene poisoning, and epoxy-resins.

The Buildings

The service's first home was a wooden hut 60 × 19 ft., provided by the Nuffield Provincial Hospitals Trust (fig. 1). Thanks to the cooperation of Mr. Eric Adams, then general manager of the Harlow Development Corporation, and Messrs. Wimpey, the capital cost of the building was only £850, with a further £600 for furnishing. Fig. 1 shows that much was packed into a very small space. The principles of the design were arrived at after studying a number of factory medical departments. Experience showed that these principles are sound, and they have been embodied in the permanent industrial health centre:

1. The *waiting-room* should be small. In industry, waiting time must be kept to a minimum, and every patient should be dealt with as soon as he arrives.

2. The *reception and record office* should communicate directly with both the waiting-room and the main surgery, so that the receptionist may prepare or get out the record card and hand it straight through a hatch to the sister on duty in the surgery.

3. The *main surgery* should be a comparatively large room with at least two treatment chairs, and a footbath. Factory medical departments sometimes have separate surgeries for men and women. In our experience, this is wasteful and unnecessary. A screen will provide privacy if needed; and patients do not undress in the main surgery.

4. The *medical room* can be quite small. It is used for patients with coughs and colds, aches and pains, and all serious casualties. Double doors and enough corridor space to move a stretcher in or out are essential.

5. A small *staff rest-room* is essential. The staff cover a period on duty of ten hours a day, and there are times when work is slack and a break is desirable. The rest-room should be near enough to the waiting-room for any arrival to be heard coming in.

6. The *store* contains not only the drugs and dressings used in the centre but also the stocks for factory first-aid boxes.

7. The *consulting-rooms* are used for full medical examinations and special clinics. Ideally, each should have an examination-room attached, or, as in the permanent centre, they should communicate so that a patient can undress in one while the history of another patient is being taken in the other.

Quite early on, a small portable X-ray machine was installed in the second consulting-room, for detecting fractures of the hands and feet, the films being developed in a member firm's dark-room. This has proved of such value that a small dark-room is incorporated in the permanent centre.

8. *Office accommodation* is kept to a minimum. But both the secretary-administrator and the medical director have to interview large numbers of people, and each must have a separate room.

Fig. 3—Permanent industrial health centre, Edinburgh House. The factory silhouetted in the background is a large glass works.

9. *Furnishing* follows that in the Trust's other health centres in Harlow. Good inexpensive modern furniture is used throughout. In the surgery modern kitchen cupboards replace the familiar metal furnishings. These look nicer and cost considerably less. In the consulting-rooms, ' Formica '-topped kitchen tables replace desks.

10. *Decoration* is predominantly white and grey with red doors. By the skilful use of colour, even a temporary wooden hut can be made very attractive inside. This has been important in attracting firms to join the service.

It will be seen that the essence of an industrial health centre is a large number of small rooms. At times, some will be unoccupied; but at other times, especially as new facilities (such as physiotherapy and orthopædic, ophthalmic, and skin clinics) are added, chaos will reign unless separate rooms are available. Moreover, emergencies tend to come in runs; then every couch may have to be made available for them.

A temporary centre like our hut will enable an indus-

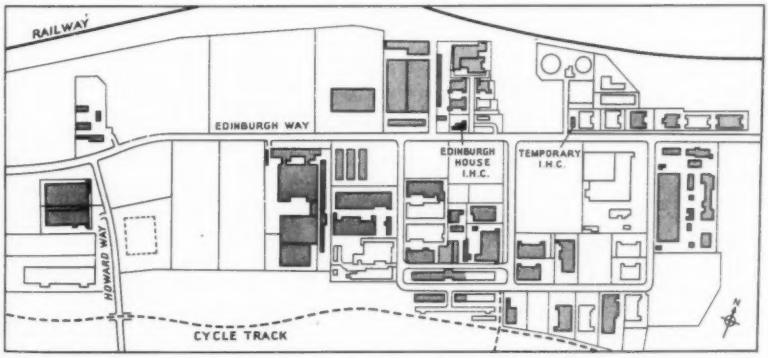

Fig. 2—Lay-out of Templefields (Eastern) industrial estate at Harlow, showing location of temporary and permanent industrial health centres. Shaded factories are members of the industrial health service.

trial health service to get under way, to gauge demand, and to prove itself. Indeed a small permanent centre, serving a working population of 3000–5000, could be constructed on precisely similar lines. But there is always the danger that temporary buildings may become permanent. At Harlow this did not arise, partly because the hut site was required by an industrialist for expansion, and partly because the Development Corporation, as area planning authority, does not normally allow temporary structures on its industrial estates. So it was necessary to press on with a permanent centre. This was started in October, 1956, and occupied in April, 1957.

The permanent centre, Edinburgh House, is located in the spine road of the industrial estate, Edinburgh Way, in the geographical centre of the estate (figs. 2 and 3). It is a single-storey building, with two garages.

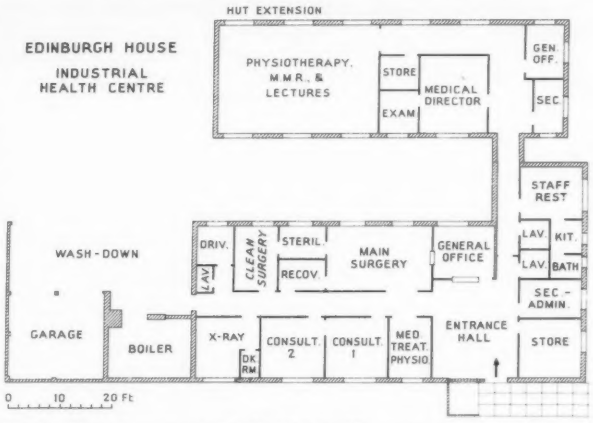

Fig. 5—Plan of permanent industrial health centre, phase 2, with hut extension. Cost £18,600.

It has oil-fired central heating. To save about £800, pipes are not ducted but carried round the walls; this is not unsightly and there have been no difficulties over cleaning, and repairs and alterations are easier.

The single-storey flat-roof construction makes it possible to have some rooms without external walls (fig. 4). These are lit either by ' Perspex ' domes or, where ventilation is required, by built-up roof lights. The windows are standard E.J.M.A.[11] wooden house-windows, which are cheap, efficient, and of sufficient variety to meet all needs. Because all rooms must be ventilated, there are no large fixed picture-windows, beloved of architects.

Throughout, the scale is slightly larger than in the hut. The main differences are the provision of:

1. A clean surgery for skin nursing, a sterilising-room, and a recovery-room.

2. A small kitchen and bathroom attached to the staff rest-room, for use by a night nursing orderly.

It was originally intended that the secretary-administrator and medical director should look after both industrial estates from an office in the town centre. When this office was released for use as part of a temporary outpatient department by the regional hospital board, other arrangements had to be made. The Nuffield Trust gave the temporary hut, to be re-erected on a more permanent basis behind Edinburgh House, to provide a large room for physiotherapy and extra consulting and office accommodation. This enabled the medical director's room in Edinburgh House (fig. 4) to be converted into an X-ray room and dark-room, and the consulting suite to be used as a duplex unit as first intended.

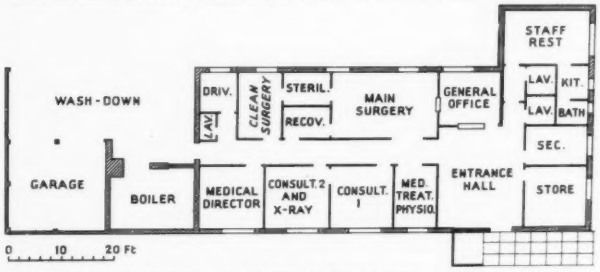

Fig. 4—Plan of permanent industrial health centre, phase 1, to serve up to 10,000 workers. Cost: £16,800 including furnishing.

The final shape of Edinburgh House, with the hut extension, is shown in fig. 5. This is, we think, an ideal unit for the care of 10,000 or more workers. The changes which have been necessary illustrate the importance of flexibility in planning and of having space available for extension.

The area of Edinburgh House (including the heating unit and garages) is 2800 sq. ft. and of the hut extension 1100 sq. ft. Costs were approximately:

	£	£
Edinburgh House:		
Main structure	12,665	
Central heating	1160	
Site, fees, furnishing	2975	
		16,800
Hut extension (including furnishing and equipment)		1800
		£18,600

The building was designed by the architectural staff of the Harlow Development Corporation (Frederick Gibberd, F.R.I.B.A., architect-planner, and Victor Hamnett, A.R.I.B.A., executive architect) (Architects-in-charge: A. McCowan, A.R.I.B.A., and M. Hughes). The contractors were Messrs. Hosking for the main building and Messrs. Leyford for the hut extension.

Records

The record system adopted is a close replica of that used in the National Health Service by general practitioners. Every patient has a card, in envelope form, with name, address, age, factory, job, and name of general practitioner on the front, and clinical notes on the back. Continuation cards, and doctors' and hospital letters are put inside. Separate cards, also to put inside, have been designed for a full medical and occupational history and for periodical clinical examinations. The advantages of this type of record are:

1. There is no need for a separate card index. The records themselves provide an index of all who have been treated.

2. They are easily handled in the surgery or consulting-room or on rounds. The contents do not fall out, as they do from an ordinary manilla file.

In addition, a day sheet is kept in the surgery, and a day book of similar design is used on the factory rounds.

Letters to practitioners and hospitals are written on special forms in tear-out books, like the familiar commercial receipt books, so that carbon copies are always available.

The whole aim has been to combine efficiency with a minimum of clerical work; this aim has been achieved.

(To be concluded)

11. The English Joinery Manufacturers' Association have a range of standard wooden windows, kitchen equipment, and cupboards.

Public Health

TOXOPLASMOSIS IN SHEEP IN ENGLAND

B. D. RAWAL
M.Sc. Bombay

From the Department of Bacteriology, University of Sheffield

TOXOPLASMA is a protozoon widely distributed among animals, including man, throughout the world. As a rule it behaves as a well-adapted, harmless parasite; only rarely does it produce disease.

In the human species it may cause severe congenital brain damage, leading to death before or after birth, or to physical and mental impairment. Less infrequently it is responsible for generalised glandular enlargement, mostly in children and adolescents; and apparently it is a common cause of posterior uveitis. (For further information see Beverley and Beattie 1958 and symposia 1955, 1956, 1957.)

Much attention has been directed to the unsolved question of the sources of human infection. The possibility that man is infected by eating infected meat is suggested by the work in the U.S.A. of Jacobs (1957), who isolated toxoplasma from the diaphragms of 11 out of 50 pigs, and in the Netherlands of de Roever-Bonnet (1957), who isolated toxoplasma from 4 out of 30 sheep brains. The object of the present investigation was to discover whether toxoplasma was present in animal carcasses in England.

Investigation

In a preliminary survey serum samples from 100 pigs and 100 sheep slaughtered at the Sheffield abattoir were examined by the dye test for toxoplasmosis (Sabin and Feldman 1948, Beverley and Beattie 1952). The sera were previously heated at 56°C for 30 minutes to obviate non-specific effects. Reactions at a titre of 1 : 4 or higher were found in 12 of the 100 samples of pig serum and in 11 of the 100 samples of sheep serum. Reactions at a titre of 1 : 64 were found in 3 of the samples of sheep serum but in none of the samples of pig serum. Attention was, therefore, directed to the examination of sheep with the particular object of isolating toxoplasms.

Blood-serum samples and brains of a further 100 sheep were obtained in seven batches of 12 and one of 16 thrice weekly during the summer of 1958. The brains were stored at approximately 4°C until the results of the dye tests were known. In most cases the period of storage was under 8 hours, but in a few it was 28 hours. 21 of the sera, unevenly distributed throughout the batches (and hence suggesting heavier infection in some flocks than in others), reacted in the dye test to a titre of 1 : 4 or more. From the corresponding brains random portions of about 8 ml. volume were ground in a mortar with 5 ml. of sterile saline solution containing 100 units of penicillin and 10 μg. of streptomycin per ml. The suspension was filtered through two layers of sterile gauze, which held back half the solid material, and after an hour in the refrigerator was inoculated intraperitoneally into groups of 4 or 6 mice. After 6–8 weeks, dye tests were done on the inactivated blood-serum of the mice and saline emulsions of their brains were examined for toxoplasma cysts.

Of the 21 sheep brains 11 produced neither antibodies nor cysts in the inoculated mice; 4 caused low-titre antibodies to appear in only 1 or 2 mice of a group. No cysts were found in their brains, nor did passage to fresh mice result in infection. The remaining 6 sheep brains, however, caused the appearance of antibodies and of cysts (see accompanying table). Toxoplasms were isolated from 1 sheep whose dye-test titre was only 1 : 4. As the amount of material inoculated into each group of mice cannot have been more than about a fifteenth of the volume of each sheep brain, the number of sheep infected may well be understated.

The cysts found in the brains of the inoculated mice had all the appearance of toxoplasma cysts; and, when inoculated intraperitoneally into mice, which received 1 mg. cortisone acetate for 2 days before and 3 days afterwards, they produced acute infection with the development of typical proliferative toxoplasms. (In mice that had not received cortisone they produced no more than asymptomatic latent infection.) Similarly when inoculated on the chorioallantoic membrane of 9-day embryonated egg they produced in 7 days typical pocks containing proliferative toxoplasms. They did not kill the embryos. Further evidence that the 6 strains isolated were true toxoplasms was obtained by preparing antigens from egg-membrane cultures and comparing them as antigens in complement-fixation tests with an egg-membrane antigen made from the RH strain. The results were similar.

RESULTS OF INOCULATION OF SHEEP BRAINS INTO MICE

Dye-test titres of sheep	Interval (hr.) between collection of brain and inoculation into mice	No. of mice inoculated	Dye-test titre of mice 6–8 weeks after inoculation	No. of cysts in brains of mice *
1 : 16	3	6	1 : 1280	1000
			1 : 320	300
			1 : 1230	1300
			3 at <1 : 4	None
1 : 229	3	6	1 : 320	304
			3 at 1 : 20	†
			<1 : 4	None
			Died	..
1 : 64	27	6	Died	800
			Killed	2000
			1 : 1280	2700
			1 : 640	1600
			1 : 2560	1600
			>1 : 320	800
1 : 4	7	4	1 : 320	120
			1 : 320	320
			1 : 640	180
			1 : 80	100
1 : 64	7	4	1 : 320	230
			3 at 1 : 4	None
1 : 128	7	4	1 : 1280	1040
			1 : 320	2800
			1 : 2560	1120
			1 : 320	640

* Estimated from number in standard volume counted under microscope.
† Cysts not seen but infection produced by passage.

Conclusion

It appears that sheep in England are infected with toxoplasma and that human infection might arise from the consumption of mutton—only, however, if it were eaten raw, for toxoplasma cysts are killed in 10 minutes at a temperature of 60°C (Rawal 1959a). That the consumption of meat in fact plays little part in the spread of toxoplasma infection to man is shown by comparison of the results of dye tests on sera from vegetarians and meat eaters in Bombay and meat eaters in Sheffield; the results are strikingly similar (Rawal 1959b). Toxoplasma infection in sheep may, however, have other importance, for Hartley and Marshall (1957) consider that in New Zealand it is a cause of ovine perinatal mortality.

I am glad of the opportunity of expressing my thanks to the superintendent of markets and the superintendent and staff of the Sheffield city abattoir. To Dr. J. K. A. Beverley I am grateful for

advice. This paper is based on part of work for the degree of PH.D. of the University of Sheffield.

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Poliomyelitis Vaccination

Requests from the public for vaccination against poliomyelitis have increased considerably in the past few weeks, and many local authorities have asked for extra supplies to augment their routine monthly order. Manufacturers are doing their best to meet this sudden demand, and emergency allocations are being dispatched. A Ministry of Health spokesman said that vaccination had never been envisaged as a "jab-on-demand" programme but as a scheme of registration followed by vaccination as soon as possible.

Dialogues of Today

AGE AND LEADERSHIP

SOCRATES: You were talking very animatedly when I came in, and now you are all silent. What were you discussing?

ERYXIMACHUS: We were considering, Socrates, whether the old have too much power.

SOCRATES: How did that question arise?

ERYXIMACHUS: Well, I commented on the health of the rulers of the nations, and Enthusiasticus here said it seemed to him shameful that the destiny of the peoples of the world should be in the hands of old men who were suffering from diseases associated with old age, which might in one way or another impair their judgment. And Apollodorus added that apart from the diseases of old age he thought it was a pity that in so many spheres of life a man has little chance of becoming a leader until he is sixty, when at the best he is likely to be cautious and conservative.

APOLLODORUS: I think, Socrates, that the value of individual experience for leadership is overrated. Before men could read and write it was important that the head of the tribe should be an old man who could remember what they did in the great flood of forty years ago, in case it should recur. But nowadays we have no need to depend on the memory of the old in order to decide on our present actions. Indeed it may be a handicap.

SOCRATES: Why, then, do you think, Apollodorus, that men choose the elderly as their leaders?

APOLLODORUS: I think the reason is obvious. It would be difficult to choose a man of forty, or even fifty, for there are too many of them, and the contemporaries of such a man would not accept him as their superior, and the old would be even less willing to do so.

ANALYTICUS: What Apollodorus says is true, but I don't think he goes to the heart of the matter, Socrates. All men carry with them through life their feelings towards their own fathers, and even when they are middle-aged they still welcome as a leader a man older than themselves, whom they can endow in their own minds with the attributes of a father. This leads them on the whole to accept his authority uncritically; but a few, who did not get on well with their own fathers, will be rebellious and critical, getting their own back upon this father-figure.

SOCRATES: If you are right about this, Analyticus, does it affect their choice of a leader in other ways, and how does the leader himself react to the situation?

ANALYTICUS: It tends to make for conservatism, Socrates. A man who is unorthodox does not present himself to the majority as a satisfactory father-substitute, and the leader in office is likely to preserve his position best if he makes as little change as possible; for those who desire change will usually be in a minority, while those who disagree with any positive course of action are likely to be many. It is only in a great emergency that a rebel becomes acceptable as a leader.

SOCRATES: You said, Apollodorus, that age tends to make a man cautious and conservative. I wonder whether Nestor, here, agrees with that.

NESTOR: The old, Socrates, have a double experience of old age; for not only are they old themselves, but, being old, they remember more old people than anyone else. I disagree with Apollodorus. It is true that some men appear more cautious and conservative as they grow older; but then such men were usually cautious and conservative before. But I have known men who were rebellious and unorthodox when they were young who showed if anything more of these tendencies as they grew older. I would say that, leaving disease on one side, age tends chiefly to exaggerate a man's characteristics. There are indeed some skills which grow better up to extreme old age, or at least no worse, as we sometimes see in artists and writers and judges, and this may be true of skill in affairs. But such men are exceptional to begin with.

ERYXIMACHUS: Apollodorus uses the term conservative as though it indicated defective judgment; but surely that is begging a very large question, for I imagine that everyone would agree that what is good should be conserved.

ENTHUSIASTICUS: I think that all such terms are out of date, Socrates. In the old days things changed little and slowly, and many good things could be achieved only by the efforts of those who saw the need for change. Then conservative and rebel meant something. But today change is occurring spontaneously so fast and so widely that these distinctions make no sense at all. Things are moving with such speed that conservatives cannot hold them back, nor rebels accelerate them. What we need in our leaders today is steersmanship. We want men who can see farther than the rest of us across the uncharted seas, and guide the ship in the right direction towards an unknown destination.

SOCRATES: That sounds very difficult. Do you think it can be done, Analyticus?

ANALYTICUS: I fancy, Socrates, that the mind has its own ways of finding answers to such problems. Certainly if it fails to do so it will be the end of us. If one thinks we are all fatalistically controlled for the rest of our lives by our behaviour as infants, one will be pessimistic about this. I personally don't think that is the whole truth, and I fancy I see signs of a new kind of leadership which can evoke and express the wisdom of a group composed of people of all ages.

SOCRATES: What do you think, Nestor?

NESTOR: When I was a young man . . .

Medicine and the Law

A Transfusion Accident

A 40-YEAR-OLD mother had severe hæmorrhage after the birth in hospital of her seventh child, and a blood-transfusion was ordered.[1] After eight pints had been given it was discovered that two of the empty bottles had pink and yellow labels respectively, instead of the blue label marking her correct blood-group. The patient died. At the inquest, a pathologist said that death was due to hæmorrhage, but it was impossible to exclude the incompatible blood as a contributory factor. The coroner remarked: "We do not know exactly what happened, but I find it difficult to see how anybody could confuse colours like yellow or pink or blue. . . . One would think that to anybody except an imbecile, the system observed at the hospital is absolutely foolproof. But it has been proved not to be foolproof and the rules could obviously be tightened up." The coroner found that the woman died from hæmorrhage accelerated by an incompatible blood-transfusion, and recorded a verdict of accidental death.

1. *Manchester Guardian*, April 15. *East Anglian Times*, April 15.

In England Now

A Running Commentary by Peripatetic Correspondents

OUR relatives certainly put us in a difficult position. Like most human beings they demand sympathy. However, I feel sure that sympathy must stop short of actual treatment or even recommendation to treatment. If they are cured, the other doctor gets the credit. If they become worse, we get the blame—and not only from the relatives.

As a keen house-surgeon, mesmerised by the power of the knife, I was the cause of procuring a partial gastrectomy for a close relation of mine. Naturally he did badly and came subsequently to vagotomy and loop anastomosis. Some months later I met his G.P. "So you're the bounder who was behind all this!" he exclaimed. "I advised him against it over the past ten years!"

But I am still not sure how a doctor can give sympathy to his relatives without becoming *engagé*. You can rarely plead—at the first mention of bunions—that you are "off duty". Because, as everybody knows, a doctor is never off duty. To the lay mind, this is one of the principles of the Hippocratic oath. However, there is one relative whom I would like to advise—and do so often without any prompting on his part. That is my father. He had a coronary and now has angina. Nevertheless he insists on doing his own paper-hanging and coal-heaving—against his own doctor's advice as well as my own. But no. His doctor "does not understand" him, and as for me, well, I am a mere boy.

* * *

The advice of the Food Standards Committee, in their report on soft drinks, calls to mind once more the value of glucose. My ignorance of the tremendous value of this sugar has long been exposed to ridicule by my better-informed and more scientifically minded patients. All too often they have drawn attention to my lack of appreciation of the importance of glucose not only in maintaining the health of the healthy but also in restoring the tissues and energies of the sick. I have, of course, recommended energy in a cheaper form, and in my ignorance have been content to rely on the enzymes of the pancreatic and intestinal juices to split off the life-giving glucose in the many starches and sugars of the 300 g. of carbohydrate ingested daily. As a matter of policy, in human relationships, however, I have learnt that I should agree to my patients' demands for a few extra grammes of glucose in aerated form, provided they pay for it out of their own pockets, which they gladly do, on reading the labels.

Surveying the ward the other day I was struck by the fact that every patient had a bottle of glucose in some form or other, paid for out of his own pocket, and I thought that perhaps I really have been rather foolish. How much better to pander to their requests and to write it up officially, if they are going to get it anyway. Even better, why not take advantage of the situation and manufacture the stuff? Why not take a really humanitarian step and provide aerated glucose in a big way. This would restore health on an equally large scale, and make puny my present efforts in treating patients singly.

In fact, I foresee a still better possibility—aerated cane-sugar:

. . . "containing not only the life-giving glucose but also the health-giving fructose, *in special chemical combination*".

But, just for the moment, I'm not revealing the name of my sucrose drink—still less its pronunciation.

* * *

Our family has produced an example of the Canute reversion complex. In the bath the other night my son, while dallying in the water, absentmindedly pulled out the plug. For some minutes he was too preoccupied to notice the departure of the water. Suddenly realising his predicament he slid over to the end of the bath, glared down the drain, and yelled "Come back!"

* * *

I wish to record my support for those who insist on the anonymity of doctors appearing in television programmes. In fact I don't think they go far enough. Many patients will recognise their doctors on the screen, so that a doctor who avoids direct publicity by withholding his name may still become the unfortunate victim of indirect publicity as a result of gossip among his patients. The simplest solution would be for doctors to wear masks, and as an additional precaution they could have hot potatoes in their mouths to disguise their voices.

* * *

When our poltergeist hurls the books from the shelves my wife says I put them away insecurely. When the saucepans fly across the room she says it's the wind. When he takes my stethoscope from the boot of the car and leaves it in the dust-bin, she says the baby did it. Any one of these explanations may be correct, but the fact that so many odd things occur in our house convinces me of the poltergeist's existence, and since my wife went away I have found definite proof.

The day after she left I arrived home and found the boiler out. It always goes out when she is away. But as the water was still hot, I decided to leave it until morning. I took a bath and went to bed. Next morning the water was still hot. I bathed again and went out without lighting the boiler. There seemed no point in getting dirty while the water was still hot. That evening it was even hotter, nearly boiling. The next day it spluttered and steamed from the taps and I had to be careful not to burn myself. Yesterday I took two long baths filled to the overflow, but today the water has been as hot as ever. Surely this will convince my wife of supernatural phenomena. She is coming home this evening and can see for herself. She can't say the baby did it, because she took him away with her.

PS.—After writing this I went to take a bath before driving to the station to meet her. But when I jumped in I found it was cold, just as cold as you would expect it to be after the boiler had been out for five days. I had to forgo my bath and go downstairs to light the boiler. I had to wash afterwards with water from the kettle.

Now I don't know whether to tell my wife or not. I can't think what explanation she will find except that I am mad, and I wouldn't like her to think that.

* * *

I'm fed up with coughs
And I'm fed up with flu,
I'm tired of my patients
I'll try something new!

I'm fed up with babies.
How I hate all their squalls!
I'm fed up with rashes
And I'm tired of night calls.

I'll take a new job,
From eight until five,
I'll sleep all the night
And in the evening I'll jive.

I'll switch off my phone
And I'll tear out my bell,
I'll only meet people
Who always keep well.

I know it will happen;
It's happened before.
I'll miss all my patients,
I'll want them once more.

I'm missing my visits,
I'm missing my phone,
I'm missing my surgery,
I feel so alone.

I can't get accustomed
To sleeping all night,
I'll refix my night bell
And then I'll feel right.

Letters to the Editor

COLLEGE OF PATHOLOGISTS

SIR,—It is an open secret that a majority of members of the Association of Clinical Pathologists have voted for the establishment of a College of Pathologists and that the views of another Pathological Body are now being sought. It has now been disclosed that the Royal College of Physicians is to have a new house near Regent's Park. Can the new premises not house a Royal College of Physicians to serve physicians and pathologists?

The pathologists' chief demand (a very necessary one in British medicine today) is for a higher qualification—not called a diploma. We are told that the membership of the Royal College of Physicians is very suitable for pathologists except for the minutiæ of physical examination. Given good will on both sides, this difficulty does not seem insuperable.

It has been urged by both physicians and pathologists that the archaic constitution of the Royal College of Physicians of London makes it unsuitable as an "appropriate" college for any specialty. This I believe to be incorrect. It is true that two changes in the constitution are needed: the enfranchisement of members to give them the same share in the government of the college as is enjoyed by the fellows; and the institution of postal voting in the election of officers. A move to new premises would seem a suitable occasion for constitutional reform. I am not ashamed of my views but prefer my opinions to be considered rather than my personality, and therefore I sign myself

XYZ.

DOCTORS FOR OVERSEAS

SIR,—Having just returned from a guest lecture-operating tour in the Middle East, may I be permitted to present another side to the very eloquent letter of Professor Nixon last week—namely, that of the Student from Overseas. From Cairo to Istanbul and Beirut to Teheran it was ever the same cry: "Cannot a place be found for one student per year in each of the twenty-odd medical schools of Great Britain?"

Provided the choice of such a man or woman was careful and approved by our local Embassy or Consul-General or maybe the representative of the British Council, and their financial background was assured, surely the strain upon our schools would be minimal.

At present vast numbers of such students are being absorbed annually by America, France, Germany, and others. Is it then asking too much of our teaching hospitals and those in power who do not think insularly and are not ashamed to act imperially to take this matter up and forthwith realise what a tremendous influence for good would be achieved not only culturally but from the point of view of prestige, and even trade, by welcoming twenty-odd foreign or Middle East medical students per annum? Provided an accepted standard of English and education has been reached and every applicant was financially secure, the students could be chosen here from a central pool each year that would not in the least interfere with that of the Commonwealth and Colonial offices. Such selection would pay untold dividends in the years to come.

London, W.1. V. B. GREEN-ARMYTAGE.

INTRAGASTRIC ADMINISTRATION OF OXYGEN

SIR,—Those of us interested in the resuscitation of the newborn infant are indebted to Dr. Apgar and her colleagues for their many scientific contributions in a field beset with empiricism. The letter in your issue of April 4 from members of this group at the New York Babies' Hospital on the effect of intragastric administration of oxygen is indeed thought-provoking.

In brief, they observed a fall of arterial oxygen saturation from 93% to 8% in a 400 g. human fœtus within 5 minutes during which only intragastric oxygen was given; a return to pulmonary oxygenation promptly restored the arterial oxygen saturation to 94%.

In the past 5 years, intragastric oxygen has gained ready and widespread acceptance as a method of resuscitation, which is surprising in view of the virtual non-existence of any objective evidence in its favour.

Although Ylppö [1] is generally credited with originating the idea, the first (and only) substantial contribution was by Åkerrén and Fürstenberg [2] in 1950. They described 7 cases and attempted to substantiate the favourable outcome by an ingenious theoretical argument. In this, it was agreed that the normal oxygen consumption is 7·5 ml. per kg. body-weight per min., or 25 ml. per min. in the average full-term infant. Then, assuming that the infant's small intestine averages 3 metres in length, adding a factor for the absorptive capacity of the stomach, colon, and rectum, and, finally, taking into consideration the extra steep gradient of high oxygen tension in the administered gas to the low arterial oxygen tension in the asphyxiated infant, Åkerrén and Fürstenberg calculate a theoretical absorption approaching that of basal requirements. Unfortunately, all this is based on a figure derived by McIver et al.[3] on injecting 25 c.cm. of air into an isolated loop of cat intestine 30 years ago. There appears to be no recent human or animal data on the transfer of oxygen in unobstructed stomach or intestine, nor any evaluation of such variables as intraluminal pressure, portal blood-flow, or the presence of mucus, meconium, and other substances. Waller and Morris,[4] who enthusiastically reported a series of infants revived by intragastric oxygen, dismissed criticism with the argument that the usefulness of the procedure could be established only by a "controlled study", understandably unjustifiable in the circumstances. But to the scientific sceptic, some objective assessment such as oximetry or even only the demonstration of a measured difference in the oxygen and carbon-dioxide content of the entering and returning gas would have been infinitely more welcome.

Physiologically, there is in fact little support for the hypothesis that the anoxic infant can be oxygenated this way. As Cook and his colleagues [5] have pointed out, the entire portal blood-flow is only a quarter of the output of the left ventricle. An equivalent reduction of pulmonary blood-flow would rapidly lead to desaturation, and of course the lung is an infinitely superior oxygenator than the gastrointestinal mucosa. Even so, for its basal oxygen requirement of 25 ml. per min., the normal full-term infant employs a minute respiratory volume of 0·5 litres of air. It is difficult to conceive how the gastrointestinal tract with neither the surface area nor the intimate alveolar-capillary architecture of the lung can assume any reasonable degree of gaseous exchange even with a minute flow of 1 litre of pure oxygen. Moreover, as pointed out by Dawes,[6] if the ductus venosus has already closed, the liver may use up any oxygen so absorbed.

It is difficult to make out from the published case-reports whether intragastric oxygen rendered infants "pink" before or after the onset of regular respiration. Certainly, in the series of

1. Ylppö, A. *Acta pædiat.* 1935, suppl. no. 17, p. 122.
2. Åkerrén, Y., Fürstenberg, N. *J. Obstet. Gynæc. Brit. Emp.* 1950, **57**, 705.
3. McIver, M. A., Redfield, A. C., Benedict, E. B. *Amer. J. Physiol.* 1926, **76**, 92.
4. Waller, H. K., Morris, D. *Lancet*, 1953, ii, 951.
5. Cook, C. D., Lucey, J. F., Drorbaugh, J. E., Segal, S., Sutherland, J. M. Smith, C. A. *New Engl. J. Med.* 1956, **254**, 562.
6. Dawes, G. *in* Recent Advances in Pædiatrics; p. 31. London, 1958.

Waller and Morris, the majority of surviving infants developed regular respiration within 1 minute of receiving intragastric oxygen. The passage of the two catheters necessary for its administration is probably the most potent sensory stimulus permissible by modern standards of neonatal care and I am personally convinced that any benefit derived from this method of resuscitation is attributable to this powerful stimulus to respiration. The insertion of a nasal catheter as far as the pharynx is equally effective.

The alleged safety of intragastric oxygen, to which its popularity can partly be attributed, also deserves comment. Obstruction of the return tube by mucus is frequent and unpredictable and a steady stream of bubbles from it does not mean that the outflow equals the inflow. A flow-rate of 3 to 4 litres, as recommended by Åkerrén, is surely inviting disaster. Distension of bowel notoriously impairs its function, particularly with regard to absorption, and one cannot help feeling uneasy about illustrations of gas-filled intestines. Moreover, interference with diaphragmatic movement of the neonate seriously hampers proper respiration. Anoxia arises from many causes and the use of intragastric oxygen in a baby with diaphragmatic hernia can prove fatal. A recent autopsy revealed multiple œsophageal and gastric erosions, some verging on perforation. The most serious objection to the administration of intragastric oxygen, however, is that it often detracts from the institution of more effective means of resuscitation, and for this reason alone it should henceforth be abandoned.

Dr. James and his colleagues are to be commended for devoting attention to the question of oxygen absorption from the gastrointestinal tract, and I await further details of their findings with great interest. Meanwhile, lest I face an accusation of unconstructive criticism, we should ponder deeply on the fact that even a 400 g. human fœtus can be adequately oxygenated from the lungs.

London, W.C.1. HERBERT BARRIE.

PRISON MEDICAL OFFICERS

SIR,—I have read with interest "Consultant Psychiatrist's" comment in your issue of April 11 on "White Slave's" letter of April 4.

One gains the impression that "Consultant Psychiatrist" believes that the general psychiatrist can undertake forensic psychiatry without any additional training or knowledge and become immediately effective in his work in a penal setting. This is of course far from being the case.

Forensic psychiatry is a highly specialised branch of psychiatry and most psychiatrists coming from outside into this field are of limited use to the authorities for some considerable time. For this specialty requires not only a grasp of penological methods but also of criminal cultures, which only some sociological knowledge can bring, together with, at any rate, some knowledge of criminology and possibly criminal law. Without this one frequently makes serious errors of judgment owing to inability to distinguish between normal behaviour in a criminal culture and psychological abnormality. Knowledge of psychogenic reactions in prison is also likely to be minimal, and this can easily lead to unnecessary demands for certification, and so on. Most psychiatrists' and psychotherapists' views are based on their experiences of middle-class values and the values of those members of the lower classes who adhere to them. In my opinion, it takes a long time to acquire a practical knowledge of the criminal population, but much could be learned from suitable training in a department of forensic psychiatry.

Whilst agreeing with "Consultant Psychiatrist" that a high standard of psychiatric practice is essential in this particularly difficult field, I think he will agree on reflection that the prison medical officer may well have more experience of the criminal than the newly joined outside consultant. I believe the final answer to this problem is in the clear recognition of forensic psychiatry as a specialty in its own right, embracing the other disciplines I have mentioned, and that psychiatrists who wish to take up this work should first embark on an additional course of training along the lines recommended at the seminar on the Psychiatric Treatment of Criminals and Delinquents, held at Copenhagen in 1958.

London, W.1. R. CEDRIC SIMPSON.

THE CHROMOSOMES OF MAN

SIR,—We note in your leading article of April 4 a genuine misunderstanding of a simple French word. Referring to our paper,[1] you say that "it is fairly certain that this extra chromosome is the result of tripling of one of the normal pairs, and not, as Lejeune et al. call it, a *supernumerary in the true sense of something quite extraneous to the normal complement*" (our italics).

We had in fact described a "chromosome supplémentaire" in mongolian cells. The French words "supplémentaire" and "surnuméraire" (the latter used in our second paper [2]) do not mean "something quite extraneous to the normal complement", but merely "supplementary" or "supernumerary". Examination of our second note to the Académie des Sciences on March 16, reporting nine cases of mongolism with a "supplementary" or "supernumerary" chromosome, would have avoided such a misunderstanding. In this note we raise the hypothesis of the non-disjunction of a small telocentric pair as an explanation of the "supernumerary" chromosome.

The linguistic troubles are more surprising since Ford et al.[3] and Jacobs et al.[4] felt there was no ambiguity attached to the term, which they translate by extra, additional, or supernumerary.

Finally it is entirely true that we have "*for reasons so far unspecified*, also thought it worth investigating mongolism". It passes our imagination that a supposedly well-authorised critic should naïvely wonder about the reasons leading to scientific achievements.

We should be grateful if we could extend through your columns our appreciation to Dr. Ford and to Dr. Court Brown for their kindness in informing us, before publication, of their beautiful work which confirms our discovery.

JÉRÔME LEJEUNE
MARTHE GAUTIER
RAYMOND TURPIN.

Hospital Trousseau, Paris.

*** The term "supernumerary chromosome" is used loosely by some to mean any kind of additional chromosome, but increasingly in the restricted sense [5] in which we employed it. Of the papers in our issue of April 4, one [4] uses it in the restricted sense, one [3] uses it more loosely. We were clearly wrong in translating Dr. Lejeune and his colleagues' term as "supernumerary", and in assuming that they might be using the word in the restricted sense we went further astray. Their second paper,[2] which was not available to us three weeks ago, makes this quite clear, and indicates that they are in substantial agreement with the British workers as to the probable nature of the 47th chromosome.

We can assure our French colleagues that no criticism lay behind our inquisitiveness about the reasons which

1. Lejeune, J., Gautier, M., Turpin, R. *C.R. Acad. Sci., Paris*, Jan. 26, 1959, 248, 602.
2. Lejeune, J., Gautier, M., Turpin, R. *ibid.* March 16, 1959, p. 1721.
3. Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. *Lancet*, April 4, 1959, p. 709.
4. Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Strong, J. A. *ibid.* p. 710.
5. White, M. J. D. Animal Cytology and Evolution; p. 156 et seq. Cambridge, 1954.

led them to look for chromosomal anomalies in mongolism. Two teams simultaneously and quite independently chose mongolism, of all possible congenital anomalies outside the "sex-reversal" group, as especially worth studying. Such an event, though far from rare, is always interesting. We own to an incorrigible and unrepentant curiosity about the diverse ways which lead people to major discoveries, and we hope that some day Dr. Lejeune will tell us how it happened.—ED. L.

CHROMOSOME COMPLEMENT IN GONADAL DYSGENESIS (TURNER'S SYNDROME)

SIR,—Dr. Ford and his colleagues (April 4) have described one case of Turner's syndrome in which the bone-marrow cells showed a complement of 45 chromosomes. This was interpreted as meaning that the patient's sex chromosomes were of the type XO.

We have investigated two typical cases of Turner's syndrome, encountered during a survey in Sweden,[1] by determining the chromosome complement of cells continuously cultivated in vitro. We found the same configuration in bone-marrow cells after a few days of culture. Also, after seven transplants, the modal number of chromosomes, 45, and the karyotype were unchanged. Furthermore, in polyploid cells, the modal count was an exact multiple of 45 and paired chromosomes could still be matched.

The same configuration of chromosomes was observed in skin cultures from both patients and it was maintained consistently after four transplantations. This established the important fact that the chromosome constitution of the skin was in agreement with that of the bone-marrow. A full report on these and other cases will follow.

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University of Uppsala, and
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Central Hospital, Eskilstuna, Sweden.

M. FRACCARO
K. KAIJSER
J. LINDSTEN.

STERILISING PRACTICE IN HOSPITALS

SIR,—In the Medical Research Council's working-party report (Feb. 28) on pressure steam sterilisers it is concluded that the modern high-vacuum steriliser "should replace many of other types" at present in use in our hospitals. Such sterilisers are standard equipment abroad and the need for their introduction on a large scale here is only too evident from the sorry tale of hospital sterilisation practice given in the Nuffield Provincial Hospitals Trust report.[2]

But under present conditions of financial stringency and high costs of such equipment, are we ever likely to see the equipment introduced into more than a fraction of our hospitals in a reasonable time? Manufacture in this country is divided between a number of small firms each producing a high-quality hand-made article by traditional "one-off" methods leading to high production costs. Were the Ministry of Health to encourage these firms to produce standard equipment in quantity by semi-mass-production methods we should expect that these costs would be greatly reduced, with the assurance that each hospital group could get an efficient and economical instrument in every case. Design principles are largely agreed upon and there is no difficulty in deciding on a few standard patterns which would meet all possible needs. At the moment it is feared that many hospital management committees are deterred from installing this essential equipment because of high costs and lack of a standard article.

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Royal South Hants Hospital,
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E. S. DUTHIE
R. A. GOODBODY.

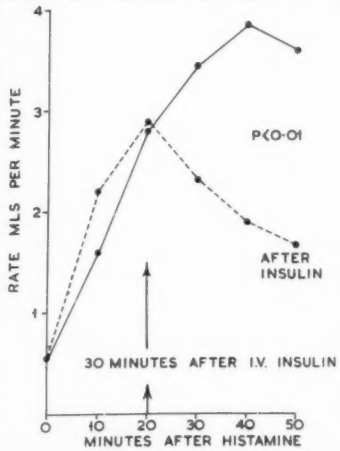
1. Kaijser, K., Enell, H., Soderhjelm, L. *Nord. Med.* 1959, **61**, 98.
2. Present Sterilising Practice in Six Hospitals. Nuffield Provincial Hospitals Trust, 1958.

GASTRIC SECRETION AND THE ZOLLINGER-ELLISON SYNDROME

SIR,—The excellent paper of Dr. Summerskill (Jan. 17) on gastric secretion in the Zollinger-Ellison syndrome has been complemented by Waddell et al.[1] on the two cases previously reported by Maynard and Point.[2] The volume and acid output of resting unstimulated gastric secretion were of the same order as obtained in duodenal-ulcer subjects when subjected to the augmented histamine tests of Kay,[3] and histamine administration produced very little further increment. Histological examination of the stomachs revealed no consistent abnormality, and a possible relative increase in the number of parietal cells is offset by the secretory data, which indicate that the non-parietal component is also secreted at the same high rate. Waddell et al. report one apparently anomalous feature in this syndrome—volume and acid secretion were depressed by insulin hypoglycæmia.

The following observations may help in explanation.

On six male volunteer duodenal-ulcer subjects an augmented histamine test was performed. One hour after the dose of histamine, 15 units of soluble insulin were administered intravenously, and ten minutes later a second equivalent dose of histamine, aspiration being continued for a further fifty minutes. In all cases blood-glucose levels below 40 mg. per 100 ml. were obtained, accompanied by the clinical features of hypoglycæmia. Collection of gastric juice was made by continuous suction, and divided into ten-minute samples, taking precautions to avoid salivary contamination. No case showed visible bile-staining of the aspirate. Estimates of acid and chloride were made by the method of Hunt,[4] and the gastric responses expressed as calculated rate of parietal secretion per minute.[5] The accompanying figure summarises the results.



Rate of parietal secretion (ml. per min.) after maximal histamine stimulation with and without insulin hypoglycæmia (means of 6).

The addition of insulin hypoglycæmia depresses the gastric secretory response to large doses of histamine in both volume and total acid output. This has previously been demonstrated in dogs,[6] and appears to depend on the limiting effect of hypoglycæmia on secretory function. The data of Waddell et al. do not conflict with the suggestions of Summerskill and of Maynard and Point that in the Zollinger-Ellison syndrome the resting stomach is

1. Waddell, W. R., Leonsins, A. J., Zuidema, G. D. *New Engl. J. Med.* 1959, **260**, 56.
2. Maynard, E. P., Point, W. W. *Amer. J. Med.* 1958, **25**, 456.
3. Card, W. I. Lecture delivered at Mount Sinai Hospital, New York, 1958.
4. Hunt, J. N. *J. Physiol.* 1949, **109**, 134.
5. Fisher, R. B., Hunt, J. N. *ibid.* 1950, **111**, 138.
6. Forrest, A. P. M., Code, C.F. *Amer. J. Physiol.* 1954, **177**, 430.

already responding almost maximally to a secretory or vascular stimulus. Although Waddell et al. invoke a hypothalamic disturbance and a vagal pathway, there is no evidence relating to the viscosity of the secretion, which might be expected to be high if a cholinergic mechanism was operating, and there is already evidence [7 8] that the resting hypersecretion of this syndrome is not greatly altered by adequate vagal section.

It is perhaps a pity that the studies again focus attention on gastric secretion in the genesis of peptic ulcer. One of the most fascinating truths revealed by study along these lines points in a different direction. An endocrine paradox exists, to which your leading article of Jan. 17 did not refer, in that women, who are less susceptible to duodenal ulcer than men, develop duodenal ulcer with a much lower gastric secretory capacity than men do.[3 9]

Gastro-Intestinal Clinic,
Sydney Hospital, Sydney,
New South Wales.

B. P. BILLINGTON.

BLOOD-VOLUME IN CHRONIC NUTRITIONAL ANÆMIA

SIR,—Dr. Tasker (April 18) has produced evidence to suggest that plasma-volume remains constant with varying degrees of anæmia, and has demonstrated that, as the anæmia becomes more severe, the hæmoglobin level reads progressively too high when compared with the total circulating hæmoglobin.

If the findings are confirmed, we ought to discard the customary hæmoglobin level, which is the ratio (hæmoglobin/whole blood-volume), and instead consider the ratio (hæmoglobin/plasma-volume), since this function would be linearly related to the total circulating hæmoglobin.

Musgrave Park Hospital,
Balmoral, Belfast.

J. ROSENSWEIG.

MUSCULAR WASTING AND CORTICOSTEROID THERAPY

SIR,—The two articles of April 4 on muscular wasting under corticosteroid therapy may leave the impression that this phenomenon is confined to the newer drugs with a fluorine radicle. Prednisone can cause wasting of the same type, as the following brief case-notes show. These two cases were not so severe as those reported by your contributors, so that it is possible that the effect of the fluorine is to exaggerate a tendency that is inherent in corticosteroids. This property of the corticosteroids has not received much attention in the literature.

CASE 1.—A woman contracted disseminated lupus erythematosus in 1952. In January, 1957, at the age of 35 she had an exacerbation and was treated with prednisone (25 mg. daily). Five months after this, and three weeks after discharge from hospital she complained that her thighs were weak. A month later they were so weak that she could walk only with difficulty; she could not squat, and she could get off the floor only by pulling herself up with a chair. The quadriceps group were obviously wasted. Since that time the dose of prednisone has been gradually reduced to 2·5 mg. o.d. in March, 1959. The thighs are much better but not normal. She was given potassium most of this time though her plasma level was normal.

CASE 2.—A man of 60 with chronic lymphatic leukæmia was given prednisone in May, 1958. The dose in the next six months varied between 20 mg. and 60 mg. daily. Four months after starting he complained of weakness, particularly in his legs. He had difficulty in using stairs. The muscles of the calf and particularly the front of the thigh were wasted. The dose of prednisone was tailed off and stopped in December, 1958. Two weeks later he said his legs were better and two months later they were normal. This patient was given potassium throughout the prednisone course.

Electromyograms were the same in both cases and the following excerpt from a report by Dr. P. Bauwens summarises the findings at the height of the disturbance:

"Exploration of the rectus femoris did not reveal any fibrillation, while on volition the motor unit pattern obtained was composed of very low amplitude short-duration potentials. The absence of frank signs of denervation coupled with the motor-unit activity pattern on volition characteristic of myopathy, point to an affection of the muscle fibre itself. This may be a muscle dystrophy or myositis".

Five tests were done on the woman which showed gradual but only partial improvement. When the man had become clinically normal the electromyogram showed that the pattern "was made up of normal potentials in most positions, but in some other positions the pattern was made up of short-duration potentials which would suggest that there is still a patchy myopathic condition although these patches are few and far between".

London, W.1.

J. B. HARMAN.

CARBROMAL INTOXICATION

SIR,—In their report of April 4 on 5 cases of carbromal intoxication Dr. Copas and his colleagues confirm the experience of several other observers, stressing the danger of habitual self-medication with this type of drug; and the *British Medical Journal* in the same week contained a description of a somewhat similar case.[1]

Confusional states arising from habitual overdosage with carbromal preparations, in particular 'Persomnia', were noted in the history and in the follow-up of our alcoholic patients on quite a few occasions. Among those alcoholics who are also prone to take any other drug to excess, persomnia seems in fact at present to be the most popular drug, sometimes taken in combination with other drugs, and the formerly popular combination of barbiturates with amphetamines has recently been replaced in some cases by the combination of the sedative persomnia with the stimulant phenmetrazine ('Preludin'). Similar cases were also occasionally seen with non-alcoholic, immature, and inadequate patients. Along with the risk of habitual overdosage there are the dangers of accidental or suicidal overdosage.

An unstable and immature male alcoholic took both persomnia and phemetrazine in increasing doses, up to 60 phenmatrazine tablets and 20 persomnia tablets in the 24 hours. His confused state necessitated admission to a mental hospital on a number of occasions.

A psychopathic, immature, and hysterical alcoholic woman became very confused and ataxic after habitual persomnia overdosage, and fell into the open fire at her home, suffering severe burns.

A middle-aged, immature, obsessional neurotic (non-alcoholic) was occasionally in a muddled condition. While in hospital, 88 persomnia tablets were found hidden in her cupboard, and she had in fact often sent another patient to the chemist with an order in a sealed envelope.

A middle-aged, immature, obsessional female neurotic bought several persomnia and glutethimide ('Doriden') containers and took approximately 12 persomnia, 16 glutethimide, and an unknown number of aspirin tablets with some alcohol in an unsuccessful suicidal attempt.

Practically all our patients habituated to persomnia and other carbromal preparations had in the past taken other drugs to excess, often in combination. That such cases are also seen elsewhere is clear from a report by Minogue and Kyneur [2] from Sydney who describe ". . . addiction to unrestricted drugs, such as carbromal, 'persomnia', chloral hydrate . . . and many others (as) far more common than is usually realised". They remark that "it is curious . . . that many of these patients are alcoholics . . ." Thus, for the great majority of people persomnia and other unrestricted drugs may indeed be

7. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
8. Dragstedt, L. R. *ibid.* p. 724.
9. Booth, M., Hunt, J. N., Miles, J. M., Murray, F. A. *Lancet*, 1957, i, 657.

1. O'Donnell Finigan, F., Kalina, M. A. *Brit. med. J.* April 4, 1959, p. 923.
2. Minogue, S. J., Kyneur, F. J. *ibid.* Jan. 24, 1959, p. 238.

"mild" and "innocuous".[3] For a small minority, however, and they are by no means always psychopaths as sometimes alleged, easy access to any sedative or stimulant drug entails the risk of habit formation. Doctors dealing mainly with selected populations, such as immature, inadequate, unstable personalities and alcoholics, will therefore sooner or later be confronted with a number of cases of habituation to any new sedative or stimulant drug. Other doctors who have less contact with this "habituation-prone" segment of the population may hardly ever come across such a case. They may therefore hold quite different views as to the need for legal restriction of the sale of such drugs. Apparently the main question is not whether certain sedative or stimulant drugs will occasionally be found to be habit-forming—they all will, in certain unstable personalities—but whether the misuse by a minority (often followed by serious consequences) justifies or necessitates the imposing of restrictions affecting also the majority who are able to use such drugs sensibly and in moderation.

St. Bernard's Hospital, Southall, Middlesex. M. M. GLATT.

SIR,—We have recently had one case where carbromal intoxication took place after a short period and where the serum-bromide was not raised at all. This is a point of some significance and it is perhaps also of interest that the *B.P.C.* lists carbromal as a prompt and safe sedative with the advantage of being less toxic than barbituric-acid derivatives.

Inverness. J. RONALD.

TRAUMA AND SQUAMOUS SKIN CANCER

SIR,—To add to Dr. Ward Gardner's list (April 11) of carcinoma following a prick, I recall an old gardener of over 80 who used to work for us off and on near Windsor. One day he appeared with a typical ulcerating epithelioma in the centre of the moustache area of his upper lip. He said that this had come on after he had pricked his lip with a thorn from a blackthorn bush while hedging. I told him to go to the local hospital where he was booked for an excision, but he got bored with waiting, and with the aid of a penknife and mirror he excised the growth himself. When I next saw him his lip had healed perfectly. I might add that I do not know whether a biopsy was done, nor do I know what was this enterprising old man's ultimate fate.

London, N.W.1. JOHN BRAY.

ASSOCIATION FOR CHILD PSYCHOLOGY AND PSYCHIATRY

SIR,—Mr. Blishen writes (March 21, p. 631) on the need for an association which will draw on all professions concerned with the welfare of children. The Association for Child Psychology and Psychiatry was founded in 1956 to meet this need. The objects of the Association are the scientific study of all matters concerning the mental health and development of children. The Association is interdisciplinary in nature, non-sectarian, and apolitical. A journal will be published from Jan. 1, 1960, devoted to this field.

I should be pleased to supply all relevant information to any person professionally concerned with children.

8, Brondesbury Court, Willesden Lane, London, N.W.2.
H. P. HILDEBRAND
Honorary Secretary, Association for Child Psychology and Psychiatry.

3. *Ibid.* 1958, i, 1176.

ALDOSTERONE EXCRETION IN NORMAL PREGNANCY AND PRE-ECLAMPSIA

SIR,—In my comment last week on the work of Dr. Kumar and his colleagues (March 14, p. 541, and April 11, p. 784) I am afraid I misquoted their results. May I explain my difficulty again?

Table III of their article of March 14 shows that in normal pregnancy at the third trimester an average of 56 mg. of aldosterone is excreted daily, and that 4·3 mEq. per litre of sodium is found intracellularly. When the aldosterone excretion *rises*, on a reduced salt intake, to a daily average of 99 μg. the intracellular sodium *falls* to 1·7 mEq. per litre. If aldosterone is responsible for increasing the amount of intracellular sodium (which the figures for group E in the same table suggest) how can one explain the previous findings in normal pregnancy of a fall in intracellular sodium in association with a rise in aldosterone excretion?

London, W.1. JOHN SOPHIAN.

THE CAUSE OF DIGITAL CLUBBING

SIR,—The reason why such a common and easily recognisable condition as clubbing of the fingers occurs is a matter of conjecture and controversy. The radiosodium-absorption studies presented by Dr. Hall (April 11) are of particular interest.

The hypothesis that digital clubbing may be due to an endocrine imbalance is criticised by Dr. Hall though he refers only to its association with pituitary involvement by carcinoma and myxœdema. The case of pituitary involvement described by Bloom [1] was a man with a carcinoma of the bronchus who developed digital clubbing, hypertrophic pulmonary osteoarthropathy, and gynæcomastia during the course of the disease. At necropsy, metastases in the anterior lobe of the pituitary gland were found, and Bloom suggested that they had excited the production of anterior-lobe hormones in sufficient quantities to produce these changes. The regression of digital clubbing which often follows lung resection, or even after the vagus nerve has been severed on the same side as the affected lung, clearly excludes stimulation of the hypophysis by metastases as a common cause. Thus on the basis of this evidence alone it is certainly not surprising that the theory that digital clubbing may be due to dyspituitarism seems untenable.

The question now to be considered is whether further evidence is available in support of the view that pituitary dysfunction may be an ætiological factor in some cases of digital clubbing.

Fried,[2] Ellman,[3] and Järvinen and Kumlin [4] described the development of digital clubbing, hypertrophic osteoarthropathy, and clinical and radiological signs of acromegaly in 8 patients with bronchogenic carcinoma. Hyperplasia of the eosinophil cells of the anterior lobe of the pituitary gland *without* any metastatic involvement of the endocrine glands was found in all 4 patients on whom postmortem examination was performed.

In a recent paper,[5] I showed that the association of gross digital clubbing and endocrine exophthalmos in patients with either postoperative or medically induced myxœdema is not so rare as might be expected from the paucity of published reports. The necropsy findings in 2 of these cases merit particular attention. One patient had an eosinophil adenoma of the pituitary gland (Greene [6 7]); the other had eosinophil hyperplasia of the anterior lobe of the pituitary (Levitt [8]).

I also described the development of severe clubbing of the fingers and toes and exophthalmic ophthalmoplegia in a patient with a toxic goitre. No other case of gross digital

1. Bloom, W. *Ann. intern. Med.* 1948, **29**, 361.
2. Fried, B. M. *Arch. intern. Med.* 1943, **72**, 565.
3. Ellman, P. *Proc. R. Soc. Med.* 1953, **46**, 851.
4. Järvinen, K. A. J., Kumlin, T. *Ann. rheum. Dis.* 1954, **13**, 52.
5. Freeman, A. G. *Lancet*, 1958, ii, 57.
6. Greene, R. *Proc. R. Soc. Med.* 1951, **44**, 159.
7. Greene, R. Personal communication, 1958.
8. Levitt, T. The Thyroid; p. 325. Edinburgh, 1954.

clubbing in untreated active thyrotoxicosis appears to have been reported previously.

The fact that gross digital clubbing is now reported in association with exophthalmic ophthalmoplegia in hyperthyroid as well as in induced euthyroid and hypothyroid states, adds, I believe, further support to the view that this syndrome, with or without pretibial myxœdema, can be regarded as a clinical manifestation of pituitary dysfunction. The importance of the role of the pituitary gland in the pathogenesis of this syndrome is still not fully understood. I would suggest that further information might readily become available if clinical assay of the anterior-lobe hormones in the serum and examination of the anterior lobe of the pituitary gland at necropsy were performed in cases of exophthalmic ophthalmoplegia with gross digital clubbing.

Victoria Hospital, Swindon. A. G. FREEMAN.

HÆMOPOIETIC EFFECT OF VITAMIN-B_{12}-PEPTIDE CONJUGATE OF LOW MOLECULAR WEIGHT

SIR,—Heathcote and Mooney [1] reported a good clinical response, in patients with pernicious anæmia, to oral vitamin-B_{12}-peptide complex derived from fermentation materials, and with a molecular weight of 10,000.

The substance used by Heathcote and Mooney is closely related to a vitamin-B_{12}-peptide conjugate (molecular weight 6500) isolated from a similar source and described by Mulli and Schmid.[2] Since 1956 this vitamin-B_{12} complex has been tested in 10 patients parenterally and in 6 orally. Intramuscularly, in doses corresponding to 20–250 μg. of free cyanocobalamin, the test material induced a clinical response comparable to peptide-free vitamin B_{12}. 7·5–10 μg. daily by mouth, with or without additional sorbitol (5 g.), was clinically ineffective. Higher doses (100–200 μg. daily by mouth) failed completely in 1 patient during a ten-day period. The bone-marrow remained megaloblastic. 2 other cases showed nearly full hæmatological remission within three to four weeks.

There is some evidence that vitamin-B_{12}-peptide conjugates with different molecular weight and different properties can be isolated, depending on the activity of proteolytic processes in the original material or the treatment with proteolytic enzymes. In earlier studies [3] vitamin-B_{12}-peptide complexes prepared from undigested cowdung and from fish press juice (a conjugate from fish press juice has a molecular weight of about 14,000) were ineffective parenterally in pernicious anæmia. These substances could be transformed into hæmopoietically active vitamin B_{12} by treatment with hog-stomach mucosa, pancreatin, or especially potassium cyanide. Vitamin-B_{12} conjugates from ox liver were clinically less active than free cyanocobalamin. The shortage of experimental material during earlier studies did not permit aminoacid analyses or a study of the effect of oral administration in pernicious anæmia. These questions are now being reinvestigated.

So far most studies on the extrinsic and intrinsic factor have considered only the binding and the absorption of free vitamin B_{12} in the intestine. The problem is complicated by the existence of vitamin-B_{12}-peptide conjugates and the action of proteolytic enzymes. The low-molecular-weight vitamin-B_{12}-peptide conjugate from fermentation material could not be transformed into free cyanocobalamin by treatment with pepsin or trypsin. Only carboxypeptidases in high concentration split off aminoacids from the peptide complex. The existence of specific vitamin-B_{12}-peptide conjugases, as suggested in earlier work, remains to be explored. Hydrogen peroxide liberates inorganic cobalt much more easily from the vitamin-B_{12}-peptide conjugate [2] than from cyanocobalamin.[4]

1. Heathcote, J. G., Mooney, F. S. *Lancet*, 1958, i, 982.
2. Mulli, K., Schmid, O. J. *Z. Vit.-Horm.-Ferm. Forsch.* 1957, **8**, 225.
3. Hausmann, K. *Lancet*, 1949, ii, 962; *Klin. Wschr.* 1950, **28**, 135; *ibid.* 1953, **31**, 1017. Hausmann, K., Mulli, K. *Lancet*, 1952, ii, 185; *Acta hæmat.* 1952, **8**, 345. Hausmann, K., Ludwig, L., Mulli, K. *ibid.* 1953, **10**, 282.
4. Hausmann, K., Ludwig, L., Mulli, K. *ibid.* 1954, **11**, 223.

Apart from theoretical questions, more clinical studies are necessary to prove that peptide binding facilitates the absorption of vitamin B_{12} through the intestinal wall.

First Medical Department, St. Georg General Hospital, Hamburg. KURT HAUSMANN.
Hamburg. KURT MULLI.

ISRAEL: THE EVOLUTION OF AN IDEA

SIR,—I am sorry to see that Dr. John (April 18) finds it necessary to perpetuate Professor Toynbee's false story of Palestinian Arabs being evicted from their homes by Nazi-minded Jews. The truth, of course, is that when Israel, on her declaration of independence, was invaded by all the neighbouring Arab States, the Palestinian Arabs were urged by the Arabs themselves to leave Palestine in the hope that, once the Jews had been thrown into the sea, the refugees could return to their homes.

Furthermore, Dr. John seems to ignore the fact that probably as many Jews had to leave Arab lands (without money or property) as there are now Arab refugees, the main difference being that Jews all over the world help their brethren to settle in Israel, while Arab countries purposely refuse to settle their own refugees, thus keeping the spirit of hate alive.

Perhaps it is not widely known that most of the money and help provided by the U.N. Specialised Agencies for Arab Refugees comes from the U.S.A. and Great Britain, none from the U.S.S.R., and very little from some of the very wealthy Arabian oil States.

Nottingham. G. FIELDING.

DIABETES INSIPIDUS WITHOUT THIRST

SIR,—Referring to the interesting article of Feb. 7 by Dr. Fourman and Dr. Leeson on thirst and polyuria and to cases of diabetes insipidus without thirst, I should like to add one which I have seen recently.

A 27-year-old man who, at the age of 12, after an injection of antidiphtheritic antitoxin, began to have episodes of tiredness, asthenia, feeling of general weakness, nervousness, mental depression, headache, and general muscular pain. During these episodes he noticed that he was dehydrated, and felt as if his face had shrunk. At 20, he spent a year in military service, his condition remaining unaltered. Not until he was 25 did a doctor discover that his daily diuresis was often around 10 litres; the patient had never mentioned it thinking that this amount was normal. He had never felt abnormal thirst, but he had discovered that the ingestion of water made him feel better; consequently he forced himself to drink it, not liking it and doing it, according to his own words, as if he were taking a remedy. Milk also alleviated his trouble, so that he had accustomed himself to drinking about 2 litres daily. He was probably in a constant state of semi-dehydration (which would explain his not feeling well). When he was treated with 5 units of pitressin tannate, the polyuria was almost immediately corrected, and a frank aversion for water developed; according to the patient, even his own saliva became repulsive. Pitressin abolished all the pre-existing symptoms, which reappeared whenever treatment was discontinued.

In relation to these cases, it is interesting to mention our observation on the thirst-suppressing or antidipsetic effect (as we believe it should be called) of pitressin in diabetes insipidus.[1] We observed that in patients with diabetes insipidus to whom water was not permitted, so that they were intensely thirsty, a pitressin injection was able to suppress thirst in 7 out of 12 cases. A dissociation of thirst and polyuria would also exist in these conditions, adding another point in favour of the existence of two separate regulating centres. The next question would

1. Pasqualini, R. Q., Codevilla, A. *Acta endocr., Kbh.* 1959, **30**, 37.

therefore be whether the antidiuretic hormone acts not only on the renal tubule to regulate diuresis but also on a hypothalamic centre to regulate thirst.

Hospital Militar Central,
Buenos Aires, Argentina. RODOLFO Q. PASQUALINI.

XANTHOMATOUS BILIARY CIRRHOSIS TREATED WITH ETHYL LINOLEATE

SIR,—Whether chronic liver disease with jaundice and xanthomatosis of skin is a clinical entity as suggested by Thannhauser and Magendantz [1] twenty-one years ago, or whether it represents an unusual response as a result of hypersensitisation to toxic agents—for instance, neo-arsphenamine—may still be undecided. It certainly is a condition suitable for a study of the effects of unsaturated fatty acids on serum-cholesterol levels.

We followed the case-report by Dr. Walker and his colleagues (Feb. 7) with great interest because it confirmed our own observations in a similar case we have followed-up over a period of eighteen months.

A married woman of 50 was admitted to hospital on Aug. 3, 1957, with a history of: weight loss for two years, pruritus for one year, intermittent discoloration of urine for a month, and jaundice for two months. There was no preceding story of hepatitis. For many years she had been drinking three to four bottles of ' Guinness ' at night.

Her general condition was fair. The skin was earthy coloured and there was jaundice of the scleræ and symmetrical xanthomatous deposits above the inner canthus of her eyes. The liver was large, hard, and not tender. The spleen was not palpable. Bile was present in the urine and urobilinogen was detectable in a dilution of 1 in 20.

Liver biopsy (fig. 1) was reported by Dr. E. H. Moorhouse as follows:

" The chief histological feature of the needle biopsy of the liver taken on Aug. 14 is a chronic inflammatory reaction in the portal areas extending into the periphery of the lobules in places. The cellular reaction consists mainly of lymphocytes together with plasma cells, mononuclear cells, and a sprinkling of neutrophil polymorphonuclears. Fibroblasts are also conspicuous, but there is minimal fibrosis or scarring and the lobular pattern of the liver is well preserved.

" There is evidence of bile stasis within the lobules and bile thrombi are seen in the finest canaliculi, especially at the periphery of the lobules, but medium and small bile ducts are hard to find, and certainly not distended. There is no evidence of new formation of bile-ducts or of lobular hyperplasia and little damage has been done to liver cells except where these are compressed and isolated by extension of the inflammatory granulation tissue."

No appreciable improvement on low-protein, low-fat, high-carbohydrate diet, insulin, and large doses of parenteral vitamin B and C was observed. She left the hospital on Sept. 23, 1957.

She was seen as an outpatient on Oct. 22, 1957.

She was readmitted on Feb. 12, 1959, complaining of severe pruritus. Xanthomatous deposits had now spread to her elbows, knees, palms of hands, fingers, and toes.

LIVER-FUNCTION TESTS BEFORE AND AFTER TREATMENT

Date	Thymol turbidity (units)	Zinc sulphate turbidity (units)	Alkaline phosphatase (units)	Serum-bilirubin (mg. per 100 ml.)	Serum-cholesterol (mg. per 100 ml.)	Corn oil	Weight
1957							st. lb.
Aug. 8	12	9	92	3·2			
,, 19	16	11	132	4·3			
,, 26	9	10	120	4·0			7 3
Sept. 9	16	7	110	4·2			7 4
,, 16	16	5	100	4·7			
Oct. 22	19	14	105	5·7	1520		7 4
1958							
Feb. 12	12	13	135	3·6	2170	½ oz. t.d.s.	
March 8					1485		
,, 12	16	12	110	2·3			7 11
,, 26	19·6	11	90	2·5	1064		
April 2					1190	1 oz. b.d.	
,, 16	9	13	110	2·6	638		
May 5	7·5	8	135	2·1	534	1 oz. t.d.s.	
,, 13					585		
,, 20					442		8 7
June 3					400		
July 8					387		
Sept. 2	7	8		1·1	350		
Oct. 28	8	10		1·2	360		8 5
Dec. 2	8	12	110	1·9			
1959							
Feb. 23	6·5	9	135	1·0	392		8 5
Mar. 13					480 (free 170, ester 310)		

We began treatment with 45 g. of corn oil containing 39% linoleic acid, but on May 5 the dose was increased to 90 g., which has been continued up to date. A gradual but steady improvement occurred, and this was supported by results of liver-function tests (see table).

She volunteered that she now felt more fit than she had for years. Her main persistent symptom was a troublesome pruritus partly controlled by promethazine hydrochloride (25 mg.) with amylobarbitone sodium (gr. 1½). The liver size and consistency remained unchanged. There was no evidence of portal hypertension. A marked decrease of xanthomatosis was noted.

A second liver biopsy (fig. 2) was reported by Dr. Moorhouse on Feb. 24, 1959, as follows:

" There was little change from that taken eighteen months previously. There is no advance in the interlobular fibrosis or extension of the damage to the liver parenchyma and indeed the cellular reaction appears to have decreased. Although the small amount of tissue made available for examination by needle biopsy entails some caution in estimating the condition of the liver as a whole, it does appear that extension of this condition has been arrested and that resolution may be occurring."

Thannhauser [2] gave his patients a diet from which all animal fat and meat was eliminated and first-class protein restricted to skimmed milk, white of eggs, and cottage cheese; and vegetable oils were recommended for cooking.

1. Thannhauser, S. J., Magendantz, H. *Ann. intern. Med.* 1938, **11**, 1662.

2. Thannhauser, S. J. Lipoidoses; p. 110. London, 1940.

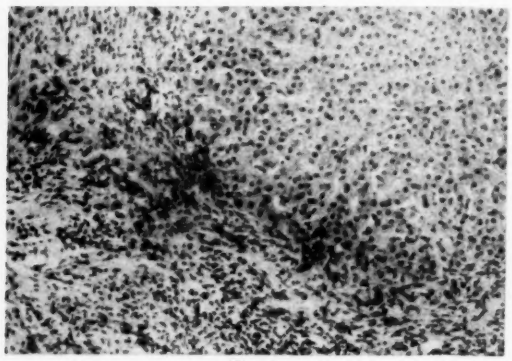


Fig. 1.

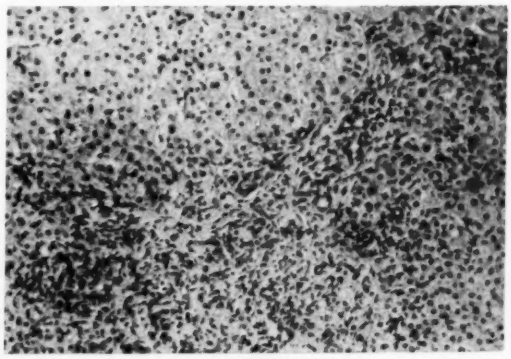


Fig. 2.

On this regime, a big decrease of total serum-cholesterols followed, particularly in a patient described in greater detail by Eusterman and Montgomery,[3] with studies of liver histology by MacMahon. In this patient the total cholesterol dropped from 1320 to 320 mg. per 100 ml. in just under a year. Liver function, however, deteriorated steadily in all cases described and hæmorrhages, ascites, infections, and liver failure supervened. In the cases described by Dr. Walker and his colleagues and in our own case, the serum-cholesterol fell almost immediately after starting treatment with linoleic acid, and within a couple of months reached levels which, with animal-fat restriction alone, were not reached until a year or so after treatment began.

H. FULD
L. HORWICH.

Liverpool.

ÆTIOLOGY OF LEUKÆMIA

SIR,—You reviewed recently [4] experimental studies dealing with cell-free transmission of mouse leukæmia. Dr. Andervont and his colleagues [5] criticised your leading article, but some of their remarks, in turn, should be corrected.

Mouse leukæmia can now be transmitted by inoculation of filtrates into newborn or suckling mice of a low-leukæmic but susceptible strain, such as C3H. The particular subline of the C3H strain used in our laboratory for the inoculation of leukæmic filtrates has an incidence of spontaneous leukæmia not exceeding 0·5%. Andervont and his colleagues claim that this figure, based on the incidence recorded in their laboratories, should read at least 10%. However, considerable variations in the incidence of spontaneous tumours have been commonly recorded in different laboratories in reference to various strains of mice and different types of tumours. Moreover, some 50% of C3H mice bred in our laboratory will also develop leukæmia following fractional total-body X irradiation. This radiation-induced leukæmia can be transmitted by filtrates to other mice.[6 7] Thus, many mice of presumably "low-leukæmic" strains may carry latent leukæmic agents; it does not surprise us, therefore, if the incidence of "spontaneous" leukæmia in mice of presumably low-leukæmic lines will vary from one laboratory to another.

This matter is, however, irrelevant. Suffice it to say that leukæmic filtrates recently developed in our laboratory by serial cell-free passage of a leukæmic agent initially derived from spontaneous Ak mouse leukæmia,[8] now induce leukæmia in up to 90% of C3H mice within 3 to 4 months of inoculation into either newborn or suckling animals of this particular strain.[9]

The statement that "Gross has in fact failed in the attempt to demonstrate infection of a strain of mice through more than one generation and the 'vertical transmission' of leukæmia virus" is not quite exact. Although vertical transmission of leukæmic agent from virus-inoculated C3H parents to their offspring could not be observed regularly, we have reported several experiments [10] in which such natural transmission of the virus actually occurred, inducing leukæmia in some of the non-treated offspring of virus-injected parents. In one experiment, the vertical transmission of the leukæmic virus could be actually followed through several successive generations of mice; eventually, however, the virus became adapted to its new host-strain, causing then only occasionally symptoms of disease.[11] A single passage of the virus from parent to offspring is compatible with the concept of vertical transmission.[12]

The comparison of leukæmia induced in mice with the virus isolated by Friend [13] to infectious mononucleosis [5] is far-fetched. Although it is realised that the disease described by Friend is different from the leukæmias that usually develop spontaneously in mice, recent studies carried out in Furth's laboratory [14] confirmed the neoplastic nature (reticulum-cell sarcoma) of this condition.

The outstanding contribution of Stewart and coworkers [15–19] rests with the fact that they have succeeded in growing, in tissue culture, the parotid-tumour virus.[15] Mouse-leukæmia filtrates contain a mixture of viruses; the leukæmic virus is distinct from that causing parotid tumours [18]; whether the same virus causes parotid tumours and other neoplasms, such as sarcomas, carcinomas, &c., remains to be determined. When the leukæmic filtrates recovered from spontaneous Ak leukæmia were grown in tissue culture, the leukæmic virus apparently did not multiply, but the parotid-tumour component multiplied, and could later on be harvested in higher titres. When inoculated into newborn mice,[15] the tissue-culture-grown virus induced parotid tumours, and several other neoplasms. Remarkably, it could also cross species; when inoculated into suckling hamsters, the tissue-culture-grown virus induced multiple sarcomas.[16] Stewart and Eddy designated this virus by the term "polyoma".[17] We prefer, however, to retain our original designation—namely, parotid-tumour virus. We have been using this term ever since this virus was originally observed in our laboratory in 1953.[18]

Andervont and his colleagues seek to spare your readers from "premature acceptance of a seemingly plausible theory" which would be "a serious hindrance to progress".[5] In medical research, as in other biological fields, there is a continuous flow of reports of new, or presumably new, facts and observations. It is very difficult to sift true progress from irrelevant and insufficiently documented data. Keen judgment and vision are required. Progress, though slow, is, however, being made. Mouse leukæmia, a disease strikingly similar to leukæmia in humans, and for years thought to be caused by genetic factors, has now been demonstrated to be caused by a transmissible filterable virus. At first seriously questioned, this new and fundamental observation, now eight years old, has been fully confirmed in several laboratories.[19–23]

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LUDWIK GROSS.

WEIGHT AND HEIGHT OF SCHOOLBOYS

SIR,—In my preparatory school of some 70 boys I have kept records of weights and heights since 1939. The increase during the past fifteen years is striking, especially in the 12- and 13-year-old groups, and reflects earlier maturity.

	Age (yr.)											
	8		9		10		11		12		13	
Average heights:	ft.	in.	ft.	in.	ft.	in.	ft.	in.	ft.	in.	ft.	in.
Jan., 1944 ..	4	3 1/4	4	4 1/2	4	6 1/4	4	8 3/4	4	11 1/2	4	11 1/2
Jan., 1959 ..	4	3 3/4	4	5 1/2	4	7 1/4	4	10 3/4	5	2 1/4	5	2
Increase ..	1/2 in.		1 in.		1 in.		2 in.		2 3/4 in.		2 1/2 in.	
Average weights:	st.	lb.	st.	lb.	st.	lb.	st.	lb.	st.	lb.	st.	lb.
Jan., 1944 ..	4	5	4	8	4	10 1/2	5	8	6	3 1/4	6	8
Jan., 1959 ..	4	8	4	13 3/4	5	0 1/2	6	0	7	1	7	4 1/2
Increase ..	3 lb.		5 3/4 lb.		4 lb.		6 lb.		11 3/4 lb.		10 1/2 lb.	

Danehill, Sussex.

L. H. MILNER-GULLAND.

3. Eusterman, G. B., Montgomery, H. *Gastroenterology*, 1944, **3**, 275.
4. *Lancet*, 1958, ii, 30.
5. Andervont, H. B., Dawe, C., Dunn, T. B., Law, L. W., Potter, M., Stanton, M. F. *Lancet*, Jan. 17, 1959, p. 154.
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20. Dulaney, A. D., Maxey, M., Schillig, M. G., Goss, M. F. *Cancer Res.* 1957, **17**, 809.
21. Hays, E. F., Beck, W. S. *ibid.* 1958, **18**, 676.
22. Kassel, R., Rottino, A. *ibid.* 1959, **19**, 155.
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DISPOSABLE RECIPIENT SETS FOR BLOOD-TRANSFUSION

SIR,—Several types of plastic disposable blood-transfusion recipient sets (" giving sets ") have recently been distributed to teaching and other large hospitals for use and comment.

As the representative of the Faculty of Anæsthetists on the subcommittee of the British Standards Institution which is considering blood-transfusion equipment, I would welcome any comments and criticisms regarding or suggestions for improvement of the disposable sets now in circulation. Perhaps readers who feel disposed to help in this way would write to me at the Department of Anæsthesia, King's College Hospital, London, S.E.5. Information supplied would be regarded as confidential and passed on to the committee anonymously after correlation.

West Ewell, Surrey. A. H. GALLEY.

TRIAMCINOLONE AND INTRACRANIAL HYPERTENSION: A SIDE-EFFECT?

SIR,—When an unusual event is associated with the use of a new drug the report of a single case may serve to alert others, so that in time the phenomenon may be recognised as an effect of the drug. Such an event has followed treatment with triamcinolone.

A child was first diagnosed as having the nephrotic syndrome in November, 1956, at the age of 4 years. Salt restriction, urea as a diuretic, and high doses of cortisone, prednisone, and prednisolone had no lasting effect, although there was a temporary diuresis with elimination of 9 lb. of surplus fluid ten days after starting cortisone. She remained extremely œdematous with a plasma-albumen level that fell as low as 0·4 g. per 100 ml. and a cholesterol level that rose to 1250 mg. per 100 ml. She developed pneumococcal peritonitis and recovered from it. Measles and Asiatic influenza both produced a short-lived remission of the nephrosis. She was treated with malaria without benefit.

After several months on prednisolone she became very " cushingoid ", with large red striæ and a bumptious personality. Variable hypertension next appeared, and the blood-pressure was once as high as 150/100 mm. Hg. Apart from albuminuria, and a few hyaline and granular casts, renal function was normal. The retinæ were normal when the blood-pressure was raised.

In March, 1958, sixteen months after the onset of the nephrosis, triamcinolone 4 mg. t.i.d. replaced the prednisolone. The result was remarkable. In ten days the œdema and albuminuria vanished, the blood-pressure fell to 110/70, the striæ started to fade, and her personality became normal. The plasma-proteins quickly rose, and the cholesterol fell. This complete remission has lasted to the present day.

Six weeks after starting triamcinolone she complained of severe morning headache, and vomited several times. Her optic fundi had been normal two weeks previously, but after she had had these symptoms for a week there was obvious papillœdema. No retinal hæmorrhage or exudate was seen, and the blood-pressure was normal. There were no signs of nephrosis, and no localising neurological signs. It was feared that after all she had been through she now was the victim of a rapidly expanding posterior-fossa tumour.

She was transferred to the War Memorial Children's Hospital, London, Ontario, under the care of Prof. J. C. Rathbun. The obvious papillœdema was confirmed. There was no clinical or biochemical evidence of nephrosis. The blood-pressure was 120/70 on admission and remained normal. The Mantoux test was negative. The cerebrospinal-fluid pressure was 580 mm. of water; the protein content and cell count of the fluid were normal. An air-encephalogram and bilateral carotid angiograms were normal. An electro-encephalogram showed much more slow-wave activity of medium to high amplitude in all regions than one would expect at this age.

From the time of transfer she was given no more triamcinolone, but had prednisone 5 mg. t.i.d. No cause for the papillœdema was found. In two weeks it had started to subside, and in four weeks it was rapidly disappearing. Two months after the onset of the raised intracranial pressure the optic discs had returned to normal.

She remains well, and apart from taking steadily decreasing doses of prednisone she leads a normal life. It is too early to speak of cure of the nephrotic syndrome (if one ever can in this condition), but it looks hopeful.

In a disease as unpredictable as the nephrotic syndrome one hesitates to attribute a remission to a particular drug, for there may be natural remissions even after months of severe disease uninfluenced by any treatment. But in this case the long remission which followed immediately upon the use of triamcinolone certainly seemed to be attributable to the drug. It is true that the related drug, prednisolone, had been used for months without great benefit and that the remission continued long after triamcinolone had been replaced by prednisone. Nevertheless, I give credit to triamcinolone for initiating a long remission in a case which was beginning to look hopeless.

I feel on firmer ground in blaming triamcinolone for the raised intracranial pressure and papillœdema that followed six weeks after starting this new drug, and which began to recede two weeks after it was stopped. The appearance of these symptoms and signs is otherwise unexplained. They are not a feature of nephrosis; and, in any event, the nephrosis was in complete remission at the time they appeared. On the other hand severe headache and dizziness has been noted as a side-effect of treatment with triamcinolone by Freyberg et al.[1] They do not mention raised intracranial pressure, but it seems both possible and tempting to suppose that the symptoms and signs here described may represent a more severe degree of the same ill-effect.

My thanks are due to Professor Rathbun of the department of pædiatrics in the University of Western Ontario for his interest in this case, and for access to his records.

University of Western Ontario, Canada. G. H. VALENTINE.

"IT'S HEALTHY TO BE HUMAN"

SIR,—You dealt generously with my book in your review of April 11, but I should like to explain two points you raise.

I omitted mention of Trotter's " herd instinct " because I was writing from a Freudian standpoint. In *Group Psychology and the Analysis of the Ego* (chapter IX) Freud writes: ". . . Trotter's exposition can be undermined psychologically; that is to say, it can be made at all events probable that the herd instinct is not irreducible, that it is not primary in the same sense as the instinct of self-preservation and the sexual instinct."

Secondly, I do not ascribe the hunting of wild dogs in packs to " intelligence subduing instinct ". In the passage to which you object I was quoting McDougall's remarks that the domesticated terrier is not intelligent enough to chase a fleeing rabbit in silence. Instead, he reverts to instinctive yapping which, in the wild state, would have summoned the pack to his aid but which usually results in the rabbit escaping its solitary pursuer.

London, W.1. F. R. C. CASSON.

1. Freyberg, R. H., Bernsten, C. A., Jr., Hellman, L. *Arth. & Rheum.* 1957, **1**, 215.

Parliament

Whole-time *v.* Part-time

IN an adjournment debate on April 14 Mr. DENIS HOWELL deplored the present tendency of consultants to change from whole-time to maximum part-time work. Between 1955 and 1957 the number of whole-time consultants had risen by only 26, though many more consultants had probably been appointed. It was difficult to supervise part-time consultants and complaints had been laid against some for laxity in ward round and outpatient clinics and for abuse of domiciliary visits. The change-over to part-time service gave the consultant the opportunity of earning private fees. As a result some private patients could obtain operations with little delay despite long N.H.S. waiting-lists. He was also perturbed because merit awards were made without consulting the board which employed the doctor and which had to find the money out of its own finances.

Mr. RICHARD THOMPSON, parliamentary secretary to the Ministry of Health, said that applications for transfer from whole-time to part-time service were not automatically granted. He agreed that part-timers had increased much more in proportion than whole-timers, but many of these were not transfers but new appointments on a part-time basis. A consultant's duties were set out in his contract with the board whose responsibility it was to assess the time required to perform them. More than once the Minister had drawn the attention of the boards to the importance of regular reviews of these assessments. When the National Health Service was first established it was generally agreed that facilities for private practice should continue to be provided, but the number of pay beds had gone down and the number of non-paying beds had gone up since the service was started. It was true that it was often easier to obtain a bed more quickly as a private patient, but in some of the larger teaching hospitals private patients had to wait longer. The numbers of private beds amounted to little more than 1% of the total bed complement and many were used in emergencies for N.H.S. patients.

Turning to merit awards, Mr. Thompson agreed that the system had some disadvantages. For example, confidential awards obscured the total amount of remuneration; and employing boards had no final voice in determining the remuneration of some of the consultants they employed. On the other hand, the system had secured higher remuneration on the basis of individual distinction rather than age or length of service. There had been some success in rewarding more than ordinary ability, and the method had met broadly with general acceptance. No superior alternative had yet been found, and the balance of advantage seemed to lie in the continuation of the arrangement.

Health in the Factories

At the report stage of the Factories Bill [1] on April 14, Mr. IAIN MACLEOD, the Minister of Labour, asked for the insertion into clause 20, which deals with the promotion of health, safety, and welfare in factories, of the following words:

> "and for the purpose of investigating such problems he may provide and maintain such laboratories and other services as appear to him requisite."

QUESTION TIME

Admission of Civilians to Service Hospitals

Civilian employees of Service departments posted abroad, and the wives and children of Service men and civilian employees whose presence at the overseas station is officially recognised, are already admitted free of charge to Service hospitals overseas. It has now been decided that, provided there is room in the hospitals, this arrangement shall be extended to wives and children whose presence is not officially recognised and to relatives or dependants who are not officially recognised as part of a Service man's family but who are living with him or visiting him, such as parents, close relations, nurses, or governesses.

1. See *Lancet*, 1958, ii, 1127.

Deaths from Influenza and Chest Diseases

The death-rates per million population from chest diseases (influenza, bronchitis, and pneumonia) for the first quarter of 1958 and 1959 were as follows:

—	London administrative county		England and Wales	
	1958	1959	1958	1959
January ..	4669	3078	3124	2214
February ..	3254	8695	2466	4721
March	2377	3961	1880	3684

Welfare Foods

In 1958 the welfare issue of orange juice and cod-liver oil was estimated to be 39% and 9% respectively of the total possible consumption.

Obituary

ERNEST FARQUHAR MURRAY

M.D. St. And., F.R.C.S., F.R.C.O.G.

Prof. Farquhar Murray, emeritus professor of midwifery and gynæcology in the University of Durham, died at his home in Jesmond, Newcastle upon Tyne, on March 23 at the age of 73.

He graduated M.B. with honours from the University of St. Andrews in 1908, and after holding resident posts in London at the Chelsea Hospital for Women and Queen Charlotte's Hospital he worked for short periods in Paris, Dublin, Berlin, and Vienna, proceeding to the degree of M.D. in 1911. Throughout the 1914–18 war, he served in the Royal Navy. He was mentioned in despatches and later retired with the honorary rank of surgeon commander R.N.V.R.

In 1921 he was appointed to the gynæcological department of the Royal Victoria Infirmary and the Princess Mary Maternity Hospital in Newcastle as assistant to Prof. Ranken Lyle. Soon afterwards he became lecturer in midwifery and gynæcology at the medical school of the University of Durham. He succeeded Professor Lyle in his hospital appointments in 1931 and in his university chair in 1935.

Professor Murray was an enthusiastic supporter of the Royal College of Obstetricians and Gynæcologists, was elected to the fellowship in 1931, and served on the council for nine years between 1929 and 1949. He was an active fellow of the North of England Obstetric and Gynæcological Society and was the first Newcastle president. He founded the Newcastle Obstetrical and Gynæcological Society with the aim of bringing the consultants and the practitioners into closer contact with modern teaching, and he helped to run regular postgraduate courses in the hospitals and medical school.

H. E. writes:

"Farquhar Murray was a man of unbounded energy and threw himself wholeheartedly into his clinical and academic work. Following in the footsteps of Professor Lyle, his teaching and practice were direct and forthright, and in the best British tradition. His lectures were instructive, entertaining, and always well attended. His contributions to his specialty were many and varied, but he was perhaps best known as the innovator of the obstetric emergency service. In the early '30s he began to be worried by the maternal deaths occurring a few hours after admission to hospital—some even in the ambulance on the way. By 1935 his ideas had crystallised and resulted in the formation of the so-called flying-squad, which brought the hospital team to the home of the woman suffering

from severe shock, especially when this was associated with the complications of the third stage of labour. The idea proved so successful that almost the whole country is now covered by over 170 squads. The saving of life has been incalculable and for this alone Farquhar Murray will always be remembered.

"He was a man of few hobbies but many friends. An excellent host, an accomplished after-dinner speaker, an entertaining raconteur, he was indeed 'a fellow of infinite jest, of most excellent fancy'; and his legion of friends, perhaps especially the members of the Gynæcological Visiting Society, will long recall his 'flashes of merriment, that were wont to set the table on a roar'".

Diary of the Week

APRIL 26 TO MAY 2

Monday, 27th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Sir Russell Brain: Consciousness and Unconsciousness.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Dr. K. M. Smith: Electron Microscopy of Viruses (Almroth Wright lecture).
HUNTERIAN SOCIETY
7.30 P.M. (Talbot Restaurant, London Wall. E.C.2.) Sir Gerald Kelly: Representational Painting—the Impression. the Portrait.
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Dr. H. T. Howat, Mr. A. Nicholson: Management of Obstructive Jaundice.

Tuesday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
3.45 P.M. Miss J. Dobson: John Hunter's Museum. (Arnott demonstration.)
UNIVERSITY OF LONDON
2 P.M. (Institute of Obstetrics and Gynæcology, Hammersmith Hospital, Ducane Road, W.12.) Prof. J. P. Greenhill (Chicago): Recent Progress in Obstetrics and Gynæcology.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. Morgan Jones, Dr. Dudley Hart, Mr. C. M. Flood: Medical Diseases in Pregnancy.
ST. MARY'S HOSPITAL MEDICAL SCHOOL
5 P.M. Mr. G. W. Theobald: Induction of Labour in Perspective.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. N. R. Mackay: Applied Physics (second of two lectures).
ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) *Medical Section.* Dr. Ian Sutherland, Mr. L. T. Wilkins, Dr. A. N. Oppenheim: Matched Pairs.

Wednesday, 29th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. J. D. Fergusson: Cysts of the Kidney.
ROYAL SOCIETY OF MEDICINE
8 P.M. *Surgery.* Discussion on the Surgical Management of Chronic Duodenal Ulcer.
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. R. E. O. Williams: Epidemiology of Streptococcal Infections.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Invasion of Keratin by Fungi In Vitro and In Vivo.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Joseph Smart: Pulmonary Physiology and its Applicability to the Treatment of Chest Conditions.

Thursday, 30th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5.30 P.M. Prof. M. A. Rushton: Cystic Conditions of the Upper Jaw.
UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Prof. Walter Modell (New York): Problems in the Evaluation of Drugs in Man.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Prof. G. M. Bull: Regulation of Body Water.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. G. A. G. Peterkin: Rare Drug Rashes.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Sir Eric Riches: The Ureter.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Small's Wynd, Dundee.) Prof. W. D. M. Paton: Mechanisms of Anaphylaxis.

Friday, 1st

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology.* Dr. Mary Sheridan, Mr. J. C. Ballantyne, Mr. R. Hunt Williams, Mr. P. S. Taylor, Mr. Daniel Ling: The Deaf Child.
2.30 P.M. *Laryngology.* Mr. G. H. Bateman, Dr. Frank Ellis, Dr. D. R. Oppenheimer: Destruction of the Pituitary for Carcinomatosis.
5.30 P.M. *Anæsthetics.* Dr. David Benazon: Development and Clinical Use of Deep Hypothermia. (Registrar's prize essay.)
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. F. N. Glover: Surgery of Parathyroid Disease.

Saturday, 2nd

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
11.30 A.M. Prof. André Djourno (Paris): Acoustic Stimulation of Nerve-fibres.

Notes and News

RESPIRATORY DISEASE IN THE PAST WINTER

AT a press conference held at the Central Middlesex Hospital on April 20, Dr. Horace Joules, medical director of the hospital, said that, for the ordinary patient, the past winter had been the worst in his 33 years' experience. The havoc wrought by cancer of the lung was threatening to outdo all the advances in the treatment of tuberculosis—in his ward recently he had had three young mothers with inoperable carcinoma of the bronchus—and mortality from bronchitis showed no sign whatsoever of falling. Ogilvie and Newell had shown that in Newcastle upon Tyne 36% of the men and 17% of the women over the age of thirty had evidence of chronic bronchitis.

Dr. Joules instanced five main causes of chronic bronchitis: (1) atmospheric pollution (especially by the non-visible sulphur gases) which was increasing, and for which power-stations and industry were largely responsible; (2) the powerfully irritant addiction of tobacco smoking; (3) dust and fumes at work, which accounted for the differential morbidity and mortality in the various social grades; (4) the influenza viruses, both known and unknown, which damaged bronchi and predisposed to the growth of staphylococci, which were often resistant to antibiotics; and (5) the overcrowding during travel to work, with its opportunities for infection.

Dr. Joules said that the Central Middlesex Hospital had virtually ceased to be a general hospital in February and March of this year. Almost all surgery had been stopped, and the only admissions had been of emergency chest and heart disease. In February, 286 such patients had been admitted, of whom 103 had died; the corresponding figures for March had been 330 and 93. On one Monday morning alone his staff had had to deal with 22 death certificates: therapeutically, the physician had often been helpless, and the hospital had many times been a mere annexe to the mortuary. Moreover, the waiting-list had had 393 patients added between Dec. 31 and March 31. Thus the medical staff would have to work overtime in the summer as well, and this was an intolerable imposition. He demanded that a Royal Commission to consider the position of preventable chest disease in this country should be established.

From his own and his colleagues' experience, a Willesden general practitioner confirmed Dr. Joules' account of respiratory disease in the past winter. Usually the hospital would accept all his emergency cases; this year less than half of them had been admitted. He thought that patients were taking a lot longer to recover than the name "24-hour 'flu" implied. Surely the time had come to attack air pollution with the same vigour as the Victorians used to attack water pollution.

Dr. H. J. Trenchard, of the Edgware Chest Clinic, had met with a similar pattern of disease. He gave details of a prophylactic scheme to get his patients with chronic bronchitis, and an exceptionally low respiratory reserve, into the country for the months of November to February.

Dr. J. D. Allan Gray, bacteriologist to the hospital, said that his laboratory had been overwhelmed by specimens of sputum for culture in this period. In the whole of 1958 he had cultured 600 resistant staphylococci; already in the first three months of this year he had cultured 300 such resistant organisms.

Dr. S. R. Craxford, head of the division of atmospheric pollution, Department of Scientific and Industrial Research, estimated that the average Londoner had about a heaped teaspoonful of matter deposited in his lungs every year. In London air (measured at Westminster) the concentration of solids was 40 mg. per 100 cubic metres of air; this might rise to 200–300 mg. in periods of peak pollution, and compared with a figure for the air in rural districts of 0–5 mg. On one day this year it had seemed that a heavy smog was inevitable—but this had been stopped by a sudden change in the weather. Even so, he had noticed that pollution-peaks this year had lasted longer than usual, although the concentration of solids in the air had been less.

In the discussion which followed, several emphasised that the height of such epidemics of chest infection coincides with the maximum sickness among the nurses; it was often difficult to make a choice between reducing nursing standards and admitting fewer patients. The enormous vested interests in air-pollution and tobacco-smoking were also mentioned; inquiry elicited that it would cost 10*s.* per ton of coal burnt to wash sulphur dioxide out of the effluents from power-stations.

REMUNERATION IN THE PUBLIC-HEALTH SERVICE

AFTER nearly a year's negotiations in Committee C of the Medical Whitley Council, new salary scales have been announced for doctors in the public-health service. The new scales, which are retrospective to last August, are:

MEDICAL OFFICERS OF HEALTH

Population group	Range of commencing salaries	Increments	Percentage increase at maximum of scale	
			Over present	Over 1951
Up to 75,000	£1930 £2195	2 × £70 2 × £65	Varies from 12·2 to 18·3	Varies from 33·3 to 36·7
75,001–100,000	£2125 £2465	2 × £70 3 × £65		
100,001–150,000	£2335 £2735	Ditto		
150,001–250,000	£2605 £3000	1 × £115 2 × £110		
250,001–400,000	£2930 £3340	Ditto		
400,001–600,000	£3065 £3605	3 × £135		
Over 600,000	At discretion	At discretion	..	..

OTHERS

Grade	Scale	Percentage increase			
		Over present		Over 1951	
		Min.	Max.	Min.	Max.
Senior medical officer	£1660 × £65–£1920 × £70–£2200	9·2	12·5	32·8	33·3
Assistant medical officer	£1150 × £60–£1510 × £65–£1640	9·4	11·2	35·3	42·6

The new agreement lays down that a deputy medical officer of health will receive two-thirds of the minimum and two-thirds of the increments of his medical officer of health. The new scale for divisional medical officers is the new scale for senior medical officers plus the following additions according to the population of the division:

Up to 150,000 .. .. £70
150,001–250,000 .. .. £200
Over 250,000 .. .. At discretion

In the circular (M.D.C. no. 42) announcing the new scales, Committee C draw the attention of all local authorities to the discretion conferred upon them by M.D.C. circular no. 9 to create posts intermediate between the grades of assistant medical officer and senior medical officer. They have also informed local authorities that M.D.C. circular no. 40 allows them to revise the salary of a medical officer in post in order to take such account as they may think fit of his professional experience obtained before joining the public-health service.

DENTISTS

Dentists employed by local authorities in Great Britain are to have their salaries increased by 10% as from Aug. 1, 1958.

The Dental Whitley Council (Local Authorities) has recommended a salary scale of £1100-£1735 for dental officers, £1790-£1845 for area dental officers, £1900-£2230 for chief dental officers (depending on population served).

A COURSE IN COMMUNITY NURSING

AN experimental nursing course is to begin in June in Manchester which will prepare students both for State registration and for the university diploma in community nursing.

The course, which is organised jointly by the university and the Crumpsall Nurse Training School, will last 4 years and 1 month. Students will spend the first 2 years and 4 months at the nurse training school and will then spend 6 academic terms at the university. They will have full university status throughout the course and they will be eligible to become members of the students' union and live in university hostels. They must live in hospital for six months during the first two years of the course. They will also be given experience of nursing in the home, the factory, and the health centre. The fee for the course is expected to be of the order of £60 p.a. and students will not receive any salary while they are working in hospital during their training.

The broad aim of teaching will be to produce a nurse for whom, in the words of Florence Nightingale, "the laws of health and of nursing are in reality the same". Thus pædiatrics and child health, obstetrics and maternal health, and the biology of infection, infectious disease, and the epidemiology of infection will be taught so as to form a natural sequence. During the final period students will join the first-year course for social administration and the course for psychiatric social workers in the department of psychiatry. Systematic lectures in midwifery, with the junior course for the medical students, will be under the direction of the professor of obstetrics and gynæcology.

DOMICILIARY VISITS

SOME eighteen months ago, in their report in the running costs of hospitals,[1] the Select Committee on Estimates recommended that the Minister of Health should inquire into the domiciliary consultative service to see if it was being misused. In a further report [2] the committee state their dissatisfaction that the Minister has so far not acted on this suggestion.

In their view the facts on which the original recommendation was based—the rise in the number of visits, especially since 1955 when whole-time specialists became entitled to remuneration, and the failure of many family doctors to attend with the consultant—make clear that some sort of inquiry is necessary both in the interests of economy and for the good name of the medical profession. They do not think that the Minister's failure to obtain the cooperation of the profession on the form of the inquiry should be a bar to any inquiry at all. They welcome the Minister's recent decision to get the basic facts from the regional hospital boards and regret that this step was not taken earlier.

On the committee's further recommendation that he should urge medical schools to examine their students on the financial structure of the N.H.S., the Minister defended his inaction on the ground that he was unwilling to appear to interfere with the independence of the medical schools. Nevertheless the Committee felt that he had a responsibility to inculcate a "sense of cost-consciousness" in the minds of all employed in the N.H.S. and might properly do more to make known his view that students should study the information on costs of prescribing which is circulated to them.

FACTS ABOUT CEREBRAL PALSY

A BOOKLET [3] published by the British Council for the Welfare of Spastics deals with the definition, ætiology, and management of cerebral palsy, and is designed to answer the questions of those whose work brings them into contact with this condition —such as teachers, physiotherapists, and social workers. Some 6000 to 12,000 children of school age are estimated to have cerebral palsy, but the number of adults affected is not known. Emphasis is laid on the special difficulties of learning and employment, and on how far these needs are met by the present special schools and workshops. The indications for surgical treatment are briefly given, and there is a valuable survey of the different methods of physiotherapy.

Despite our increased appreciation of the difficulties which beset those with cerebral palsy, the delay between diagnosis at a hospital and regular planned treatment is still serious in many cases. As the pamphlet wisely observes, charity and open minds are needed more than anything else to mitigate the present confusion.

1. See *Lancet*, 1957, ii, 739.
2. Fifth Special Report from the Select Committee on Estimates. Session 1958–59. H.M. Stationery Office. Pp. ix + 18. 2*s*.
3. Some Facts About Cerebral Palsy. British Council for the Welfare of Spastics, 13, Suffolk Street, Haymarket, London, S.W.1. 1959. Pp. 20. 1*s*. 6*d*.

University of London

Dr. Sheila Sherlock, lecturer in medicine at the Postgraduate Medical School of London, has been appointed to the chair of medicine at the Royal Free Hospital School of Medicine.

Dr. Sherlock graduated M.B. with honours and the Ettles scholarship in 1941 from the University of Edinburgh. She spent a year as assistant to Sir James Learmonth in the department of surgery before she went to the Postgraduate Medical School. In 1945 she was awarded the gold medal for her M.D. thesis. In 1947 she spent a year in the United States with a Rockefeller fellowship at Yale University. In her present appointment at Hammersmith she has done much original work on hepatic disorders—especially hepatic coma—and the second edition of her book on *Diseases of the Liver and Biliary System* was published last year. She was elected F.R.C.P. in 1951 and F.R.C.P.E. in 1959.

National University of Ireland

On April 16 the degree of M.D. was conferred on S. M. Shea. The following appointments were made:

University College, Cork.—J. D. Sheehan, professor of physiology; R. A. Daly, lecturer in clinical pathology.

University College, Galway.—E. M. O'Dwyer, professor of obstetrics and gynæcology; J. M. Lavelle, professor of experimental medicine and practical pharmacology; J. K. Burns, lecturer in physiology; M. G. A. Little, lecturer in medical jurisprudence; Brian McNicholl, lecturer in pædiatrics; B. J. O'Driscoll, lecturer in therapeutics; C. F. McCon, lecturer in preventive medicine.

British Society for Immunology

This society will hold a meeting at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, on Friday and Saturday, May 8 and 9. The programme will include a symposium on delayed hypersensitivity. Further particulars may be had from Dr. R. G. White, The London Hospital, E.1.

Rockefeller Foundation Grants

During the first quarter of 1959 the Foundation distributed $2,300,000. Grants for medical education and public health amounted to $153,500, and for biological and medical research $780,000. The grants included a further $41,000 (the Foundation made a grant of $156,000 in 1955) for biochemical research on mental disease which is being carried out at the University of Oxford under Sir George Pickering. The new grant is to go towards a five-year study on the body fluids of schizophrenics by partition chromatography and electrophoresis by a group of Medical Research Council workers under Dr. Ian Bush.

Society of Chiropodists

At the society's annual dinner in London on April 16 the toast of The Profession was proposed by Dr. J. A. Scott, medical officer of health for the county of London. Speaking of his earnest hope that the Government will give proper recognition to this important group of medical auxiliaries by introducing statutory registration forthwith, he said that this is especially desirable now that extension of the chiropody service under the National Health Service is imminent.

Responding, Mr. John R. Hall, the president, said that the society has always hoped for a national chiropody service, and he thought that priority should be given, irrespective of age, on medical grounds as defined by general practitioners. This would ensure that those most in need are treated first; it would check the demand (for at present the number of chiropodists available is likely to be too small); and it would encourage cooperation between the doctor and the chiropodist. The question of how the service should be operated remains to be settled, but where clinics are not established it is desirable for the work to be done in private surgeries. There are, Mr. Hall said, many more problems, but he felt confident that the present difficulties will be overcome, and that chiropodists can look forward to an expanding, prosperous, and healthy tomorrow.

Miss M. R. Witting, member of the council of the society, proposing The Guests, particularly welcomed Lady Webb-Johnson whose husband had done so much for chiropody. Dr. H. Seaward Morley, member of the General Medical Council, responded for the guests, most of whom were members of the medical profession.

University of Sydney

Dr. Nicolas Malleson, physician in charge of the student health service of University College, London, has been appointed the first director of the student health service at the University of Sydney.

Reorganisation of French Medicine

The earlier resistance of the medical profession in France to the reform of the medical curriculum and the creation of university hospital centres [1] has been renewed. On April 14 the syndicats médicaux and on April 15 the Académie de Médecine passed resolutions against the proposals.

Russian Lectures in Education

On May 4; 5, and 8, at 5.30 P.M., Prof. I. A. Kairov, president of the Academy of Pedagogical Sciences of the R.S.F.S.R., Moscow, will lecture at the University of London Institute of Education, Malet Street, W.C.1. He will speak on basic elements of moral education in the general secondary school in the Soviet Union, education of students in the spirit of patriotism, peace and friendship amongst the nations, and moral education of children in a group. The lectures will be delivered in Russian and translated into English by an interpreter.

Dr. S. L. Morrison will give a lecture on epidemiology and mental illness on Monday, May 4, at 8.15 P.M., at Marlborough Day Hospital, 38, Marlborough Place, London, N.W.8.

A clinico-pathological conference will be held on Friday, May 8, at 5.30 P.M. at the Westminster Hospital Medical School, Horseferry Road, S.W.1, on aortic coarctation.

Dr. F. J. G. Jefferiss has been appointed honorary civil consultant in venereology to the Royal Air Force in succession to Dr. G. L. M. McElligott who is retiring.

Dr. E. R. Boland has been re-elected chairman of the Central Medical Recruitment Committee.

The general director of the Y.W.C.A. Central Club (Great Russell Street, London, W.C.1) asks us to remind doctors that the accommodation at this club is unsuitable for people recovering from mental or physical illness and that it should not be recommended for convalescence.

The Academy of Physicians and Surgeons, which was formed in Singapore last year, has changed its name to the Academy of Medicine. The academy draws its members from all specialties of medicine and dental surgery, and it was felt that the original name might suggest that the members were only physicians or surgeons.

1. Delafresnaye, J. F. *Lancet*, April 11, 1959, p. 771.

Appointments

BLUNDELL, J. A., M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Aylesbury/High Wycombe area.

CAITHNESS, G. S., M.B. Dubl.: medical records and admitting officer, Guy's Hospital, London.

JONES, R. J., M.B., B.SC. Wales, D.OBST.: assistant M.O.H. and school M.O., Chester.

LIVINGSTONE, DUNCAN, L.R.C.P.E., D.I.H., D.P.H.: depute M.O.H., Inverness.

SASIENI, R. DAPHNE R., M.B. Brist., D.OBST., D.P.H.: deputy M.O.H., Benfleet, Canvey Island, Rayleigh, and Rochford.

WARD, G. W., M.B. Manc., D.P.H.: senior school M.O., Cornwall.

East Anglian Regional Hospital Board:

ALMANI, M. A., M.B. Pakistan: medical registrar, Peterborough hospital group.

DAY, D. E., M.B. Lond.: anæsthetic registrar, West Suffolk General Hospital.

HUNTING, HILDA M., M.B. N.U.I.: anæsthetic registrar, Peterborough Memorial Hospital and annexes.

YANEZ, L., Med. Dip. Madrid: surgical registrar, Stamford and Rutland Hospital.

Births, Marriages, and Deaths

BIRTHS

OWEN.—On April 15 at Newcastle upon Tyne, to Dr. Ruth Owen, wife of Dr. S. G. Owen, a son—Mark Lawton.